Review Article

Adverse events related to blood transfusion

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ABSTRACT

The acute blood transfusion reactions are responsible for causing most serious adverse events. Awareness about various clinical features of acute and delayed transfusion reactions with an ability to assess the serious reactions on time can lead to a better prognosis. Evidence-based medicine has changed today's scenario of clinical practice to decrease adverse transfusion reactions. New evidence-based algorithms of transfusion and improved haemovigilance lead to avoidance of unnecessary transfusions perioperatively. The recognition of adverse events under anaesthesia is always challenging. The unnecessary blood transfusions can be avoided with better blood conservation techniques during surgery and with anaesthesia techniques that reduce blood loss. Better and newer blood screening methods have decreased the infectious complications to almost negligible levels. With universal leukoreduction of red blood cells (RBCs), selection of potential donors such as use of male donors only plasma and restriction of RBC storage, most of the non-infectious complications can be avoided.

Key words: Adverse events, anaesthesia, blood transfusion, complications, non-infectious

INTRODUCTION

An adverse reaction or event is an undesirable response or effect in a patient, temporally associated with the administration of blood or blood component.[1] Now-a-days, even in developed countries, the greatest risk to the patient lies in non-infectious complications of transfusions that account for significant morbidity and mortality.[2] In this review, the non-infectious adverse events related to blood transfusions aere defined as non-infectious adverse transfusion reactions (NIATRs). The American Association of Blood Banks technical manual provides guidance for the recognition, diagnosis, investigation and classification of non-infectious transfusion reactions, which can serve as a ready reference for clinicians and other health care providers dealing with blood transfusion.[3] The acute and delayed NIATRs are classified on time of occurrence and further divided by presumed aetiology into immune-mediated and non-immune mediated subtypes. An overview of various common NIATRs comprising the classification, pathophysiology, clinical presentations, and management is presented in Table 1. As an aid to help the clinicians in a suspected NIATR, an approach to differential diagnosis is being provided in Figure 1. The broadly accepted classification of the adverse reactions as follows:

ACUTE NON-INFECTIOUS BLOOD TRANSFUSION ADVERSE REACTIONS

Occurring within 24 h after transfusion, they are classified as Acute immune mediated blood transfusion reactions and Acute Non- immune mediated – blood transfusion reactions. Acute immune mediated – blood transfusion reactions are further sub-classified.

Acute haemolytic transfusion reactions

A haemolytic transfusion reaction is one in which symptoms and clinical or laboratory signs of increased red cell destruction are produced by transfusion. In acute haemolytic transfusion reactions (AHTRs) symptoms appear within minutes after starting the transfusion. Common laboratory features are haemoglobinemia, haemoglobinuria, decreased serum haptoglobin, unconjugated hyperbilirubinaemia, increased Lactate dehydrogenase and serum glutamic-oxaloacetic transaminase levels and

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Table 1: An overview of important noninfectious adverse transfusion reactions (modified from AABB technical manual)[3]

Type	Pathophysiology	Clinical presentation	Management#
Acute (occurring<24 h after transfusion)			
Immune mediated			
Acute haemolytic transfusion reaction	Red blood cells mismatch between donor and recipient	Fever, chills/rigors, back pain, hypotension, haemoglobinuria, pain along IV line, bleeding diathesis	Stop transfusion and keep IV line open; maintain urine output>1 ml/kg/h and IV diuretic; analgesics; low-dose dopamine for hypotension; blood components for bleeding
Febrile nonhaemolytic transfusion reaction	Cytokines in blood unit	Rise in temperature>1°C, chills and/or rigors, discomfort, vomiting, flushing	Antipyretics (acetaminophen but not aspirin); meperidine for rigors; use of leukofiltered blood components
Urticarial	Recipient's IgE react with donor plasma protein leading to release of mast cell mediators	Pruritus, urticaria, or flushing	Antihistamine treatment or premedication; restart unit slowly after antihistamine if symptoms have resolved
Anaphylactic	Antibodies to donor plasma proteins including IgA, haptoglobin, complement, ethylene oxide	Hypotension, urticaria, bronchospasm, stridor, local oedema	Adrenaline 0.5 ml of 1:1000 solution (500 μg) SC or IM in adults; in severe cases, 1:10,000 IV, initial rate 1 μg/min; antihistamines (10 mg of chlorphenamine IM or IV), corticosteroids (200 mg of hydrocortisone IM or IV); washed or IgA-deficient blood components
Transfusion related acute lung injury	Leukocyte antibodies in donor or recipient	Hypoxemia, noncardiogenic pulmonary oedema, respiratory failure, hypotension, fever, cyanosis	Treatment may range from oxygen to ventilator support
Non immune mediated			
Transfusion related sepsis	Blood products contaminated with bacteria	Fever≥102°F, chills, hypotension within 90 min of transfusion	Antibiotics and management of shock; bacterial culture; pathogen inactivation of blood components
Non immune haemolysis	Physical/mechanical/ chemical destruction of blood (*in vitro* haemolysis)	Features of intravascular haemolysis of red cells, namely, haemoglobinuria, haemoglobinemia	Symptomatic treatment
Transfusion associated circulatory overload	Volume overload in susceptible patients	Signs of congestive heart failure, shortness of breath, wheezing, hypertension	Diuretics; oxygen; phlebotomy; careful monitoring of transfusion flow rates
Air embolism	Air infusion via IV line (open system)	Sudden dyspnoea, acute cyanosis, shoulder or back pain, cough, hypotension	Left trendelenberg position; aspiration of air; possibly priming of all lines before connection
Delayed (occurring>24 h after transfusion)			
Immune mediated			
Delayed haemolytic transfusion reaction	Anamnestic immune response to red cell antigens	Fever, decreasing haematocrit, mild icterus with other features of haemolysis	Crossmatch compatible unit to be transfused after identifying red cell antibody
Alloimmunization to red cell antigens, platelets and leukocytes (HLA)	Immune response to red cells, platelets, leukocytes antigens	Haemolytic disease of fetus and newborn, delayed serologic reaction, platelet refractoriness	Rational use of blood components; leukofiltered blood
Transfusion associated immunomodulation	Allogeneic leukocytes or their soluble products	Increased chances of postoperative infections, cancer recurrence, multiple organ dysfunction	Leukofiltered blood, autologous blood
Transfusion associated graft versus host disease	Engraftment and multiplication of donor lymphocytes in the recipient leading to host tissue destruction	Rash, watery diarrhoea, fever, anorexia, vomiting, abnormal liver function tests, bone marrow failure	Corticosteroids; cytotoxic agents; irradiation of cellular blood components
Posttransfusion purpura	Antibodies against platelet specific antigens	Thrombocytopenia, purpura, bleeding	Steroids; IVIG; plasmapheresis; avoid platelets
Non immune mediated			
Iron overload	Iron deposition in a multi-transfused patient	Diabetes, cardiomyopathy, cirrhosis	Iron chelating agents

IV – Intravenous; IM – Intramuscular; SC – Subcutaneous; HLA – Human leukocyte antigen; IVIG –Intravenous immune globulin

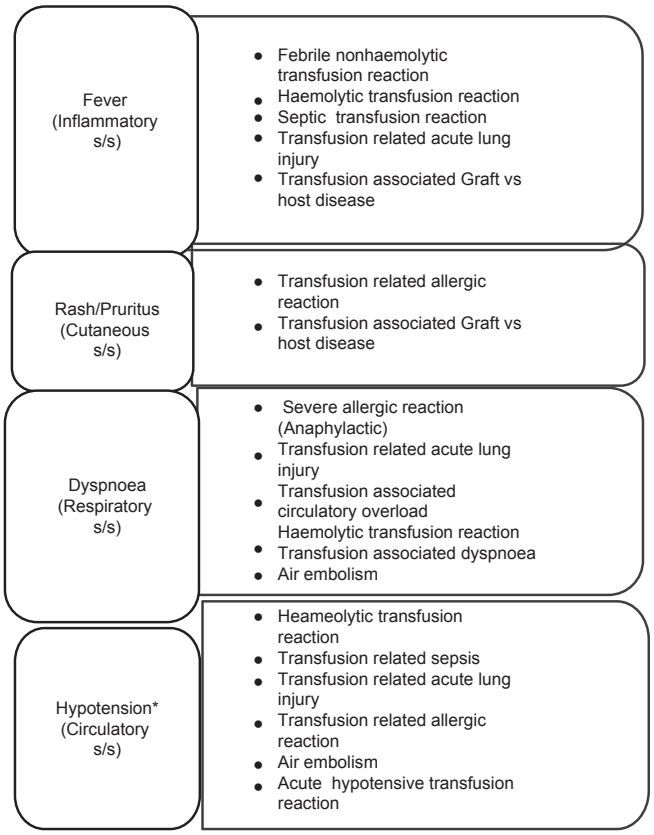

Figure 1: Differential diagnosis of adverse transfusion reactions based on clinical presentation (s/s, signs and symptoms). It is common to find overlapping symptoms in most patients.*Severe Hypotension can progress into shock

decreased haemoglobin. The interaction of recipient's preformed antibodies with donor's red cell antigens resulting in immediate destruction of the transfused red cells is the immunologic basis for AHTRs. Rarely, transfusion of ABO-incompatible plasma (e.g. ABO mismatch platelet transfusion) can cause haemolysis of the patient's red cells especially if donors have high titer of ABO antibodies. AHTRs and related mortality have been reported to occur at approximately 1 in 76,000 and 1 in 1.8 million units transfused, respectively.[3] Guidelines for identifying and managing accordingly for acute transfusion reactions, adapted from WHO guidelines use of blood during surgery and anaesthesia had been described in Table 2.[4]

Febrile nonhaemolytic transfusion reactions

Febrile nonhaemolytic transfusion reactions (FNHTRs) are characterised by an otherwise unexplained rise in temperature of at least 1°C during or shortly after transfusion. Antipyretic premedications may mask a fever, but they do not usually prevent chills and rigors, which are due to cytokine mediated systemic inflammatory response. Other causes of fever should be excluded before making a diagnosis of FNHTR. FNHTRs are seen more often after transfusion of platelets (up to 30% of platelet transfusions) than red blood cells (RBCs) because platelets are stored at room temperature, which promotes leucocyte activation and cytokine accumulation.[5] Treatment of FNHTRs is symptomatic. The prestorage laboratory leucoreduction is useful and is more effective than bedside leucoreduction.

Allergic reactions

Symptoms may either occur within seconds or minutes of the start of transfusion or may take several hours to develop.

Urticaria

Urticaria is the mildest form of an allergic reaction that appear suddenly, usually causes itching and can last for hours or up to several days before fading. More extensive cases may be accompanied by angioedema. The incidence of urticaria is 1-3%.[3,6] Once the symptoms subside, the transfusion may be resumed. Severe reactions may be managed with methylprednisolone (125 mg intravenously) or prednisone (50 mg orally).

Anaphylaxis

Anaphylaxis is a more severe form of an allergic reaction with an incidence of 1:20,000-1:50,000 transfusions,[7] in which severe hypotension, shock, and loss of consciousness may occur.[8] Anaphylaxis is commonly seen in IgA deficient recipients where it is caused by antibodies against donor IgA. Patient antibodies against haptoglobin penicillin, the C4 determinant of complement and ethylene oxide have all been implicated in the causation.[9] The term 'anaphylactoid' is used for reactions with symptoms similar to anaphylaxis but which are not mediated by IgE. If the patient is unconscious or in shock, inj. adrenaline may be given intravenously with cardiac monitoring.[10]

Transfusion related acute lung injury

Transfusion related acute lung injury (TRALI) is a form of acute lung injury (ALI) and is an important cause of transfusion-associated morbidity and mortality. TRALI has been defined as:[1]

- Acute lung injury with hypoxemia and $PaO_2/FiO_2 \leq 300$ or $SpO_2 < 90\%$ on room air
- Bilateral pulmonary oedema on frontal chest radiograph
- No evidence of left atrial hypertension
- No pre-existing ALI before transfusion
- Onset of symptoms within 6 h of transfusion
- No temporal relationship to an alternative risk factor for ALI.

Table 2: Guidelines for identifying and managing accordingly for acute transfusion reactions, adapted from WHO guidelines use of blood in surgery and anaesthesia[4]

Category	Symptoms for recognition	Immediate management to be done
Category 1	Mild symptoms	Slow the transfusion
	Localized cutaneous reactions	Administer antihistamines IM (e.g., chlorpheniramine 0.1 mg/kg or equivalent)
	Urticaria, rash	If no clinical improvement within 30 min or if signs and symptoms worsen, treat as category 2
	Pruritus (itching)	
Category 2	Moderately severe	Stop the transfusion. Replace the infusion set and keep IV line open with normal saline
	Flushing	Notify the doctor responsible for the patient and the blood bank immediately
	Urticaria	Send blood unit with infusion set, freshly collected urine (for Hb) and new blood samples plain vial (1 clotted and 1 anticoagulated) from vein opposite infusion site with appropriate request form to blood bank and laboratory for investigations (compatibility testing, ABG, antibody IgA level EDTA vial), CBC, renal and liver function, LDH, blood culture, coagulation screening, direct antiglobulin test)
	Rigors	
	Fever	
	Restlessness	
	Tachycardia	Administer antihistamine IM and oral or rectal antipyretic (e.g., paracetamol 10 mg/kg: 500 mg – 1 g in adults). Avoid aspirin in thrombocytopenic patients
	Anxiety pruritus (itching)	
	Palpitations	Give IV corticosteroids and bronchodilators if there are anaphylactoid features (e.g. broncospasm, stridor)
	Mild dyspnoea	
	Headache	Collect urine for next 24 h for evidence of haemolysis and send to laboratory
		If clinical improvement, restart transfusion slowly with new blood unit and observe carefully
		If no clinical improvement within 15 min or if signs and symptoms worsen, treat as category 3
Category 3	Life threatening	Stop transfusion. Replace the infusion set and keep IV line as above
	Rigors	Infuse normal saline (initially 20-30 ml/kg) to maintain systolic BP. If hypotensive, give over 5 min and elevate patient's legs
	Fever	
	Restlessness	Maintain airway and give high flow oxygen by mask
	Hypotension (fall of≥20% in systolic BP)	Give adrenaline (as 1:1000 solution) 0.01 mg/kg body weight by slow IM injection
	Tachycardia (rise of≥20% in heart rate)	Give IV corticosteroids and bronchodilators if there are anaphylactoid features (e.g., broncospasm, stridor)
	Haemoglobinuria (red urine)	
	Unexplained bleeding (DIC)	Give diuretic: E.g., frusemide 1 mg/kg IV or equivalent
	Anxiety	Notify the doctor responsible for the patient and the blood bank immediately
	Chest pain	Send blood unit with infusion set, fresh urine sample and new blood samples as above
	Pain near infusion site	Check a fresh urine specimen visually for signs of haemoglobinuria (red or pink urine)
	Respiratory distress loin/back pain	Start a 24 h urine collection and fluid balance chart and record all intake and output. Maintain fluid balance
	Headache	
	Dyspnoea	Assess for bleeding from puncture sites or wounds. If there is clinical or laboratory evidence of DIC, give platelets (adult: 5-6 units) and either cryoprecipitate (adult: 12 units) or fresh frozen plasma (adult: 3 units). Use virally-inactivated plasma coagulation products, wherever possible
		Reassess. If hypotensive
		Give further saline 20-30 ml/kg over 5 min
		Give inotrope, if available
		If urine output falling or laboratory evidence of acute renal failure (rising K^+, urea, creatinine)
		Maintain fluid balance accurately
		Give further frusemide
		Consider dopamine infusion, if available
		Seek expert help: The patient may need renal dialysis
		If bacteraemia is suspected (rigors, fever, collapse, no evidence of a haemolytic reaction), start broad-spectrum antibiotics IV, to cover pseudomonas and gram positive

If an acute transfusion reaction occurs, first check the blood pack labels and the patient's identity. If there is any discrepancy, stop the transfusion immediately and consult the blood bank. BP – Blood pressure; DIC – Disseminated intravascular coagulation; IM – Intramuscular; Hb – Hemoglobin; ABG – Arterial blood gas; EDTA – Ethylenediaminetetraacetic acid; CBC – Complete blood count; LDH – Lactate dehydrogenase; IV – Intravenous

Possible TRALI is also defined using the same criteria as for TRALI, however, in the setting of an alternative risk factor for ALI. The lung injury in TRALI is most often transient, and approximately 80% of affected patients will improve within 48-96 h.[3] Unlike Transfusion associated circulatory overload (TACO), pulmonary oedema in TRALI is noncardiogenic and is not improved by diuretic therapy. TRALI is a clinical diagnosis; laboratory data may only support the diagnosis. TRALI is the new onset or worsening of pulmonary function with hypoxemia that satisfies the international criteria for ALI (PaO_2/FiO_2 <300 mmHg), with a chest X-ray consistent with pulmonary oedema occurring during or 6 h within transfusion.[11] All

plasma-containing components, including whole blood, RBCs, platelets, cryoprecipitate and fresh frozen plasma, have been implicated in TRALI. The incidence of TRALI has been estimated to be approximately 1 in every 5000 blood component transfusions. Antibodies can be formed against leucocytes (polymorphous neutrophil [PMN]), both for neutrophils and human leucocyte antigen after exposure to foreign antigens via pregnancy, transfusion, or transplantation. Two different aetiologies have been proposed.[12] It can be a single antibody-mediated event involving the transfusion of anti-human leukocyte antigen (HLA) or antigranulocyte antibodies into patients whose leukocytes express the cognate antigens. In the majority of cases with antibodies, the source of the antibody is the donor, not the patient. A two-event model of the mechanism of TRALI has also been proposed leading to neutrophil activation resulting in pulmonary endothelial damage, capillary leakage, and pulmonary oedema. With prompt respiratory support marked clinical improvement can occur within 48-96 h.[13]

Applying consistent transfusion guidelines may decrease unnecessary transfusions and its morbidity. In addition, many investigators, transfusion medicine professionals, and the American Association of Blood Banks advocate temporary disqualification of donors implicated in TRALI reactions until leucocyte antibody testing can be completed. If these donors have antibodies to high-frequency leucocyte antigens, they should be disqualified from plasma or platelet donation. To make the blood supply safer, the United Kingdom (UK) has disqualified all multiparous females from plasma donation because of the possibility that plasma from females may be a major factor in TRALI. For scheduled major surgical procedures requiring transfusions, washing of cellular components removes antibodies, lipids, and other biologic response modifier from the plasma fraction. Using packed red blood cells (PRBCs) for <14 days and platelet concentrates for <2 days may avert many of the effects of these compounds, which accumulate during storage because there is no significant accumulation of PMN priming activity during shorter storage times for PRBCs and platelet concentrates, respectively. For future considerations, patients who are at increased risk for developing TRALI may include therapies such as anti-platelet agents and alternatives to traditional blood components such as prothrombin complex concentrates.[14]

Management of TRALI

Treatment is largely supportive.Effective measures for decreasing the incidence of TRALI include the use of predominantly male plasma and apheresis platelets. Greater understanding of the blood component and patient risk factors for TRALI will hopefully lead to novel treatment and preventive strategies for reducing the risk of this life-threatening syndrome. TRALI management consists mainly of preventing future adverse reactions.[15] A patient in whom TRALI is suspected should be reported to the National Blood Bank for a serological workup of the recipient and the implicated donors on the presence of HLA and HNA antibodies. Incompatibility is tested by cross-matching donor plasma against recipient's leucocytes. A donor with antibodies which are incompatible with the patient is excluded from further donation of blood for transfusion products.

Acute non-immune mediated adverse reactions

Transfusion related sepsis

Although uncommon, transfusion-related sepsis can be fatal. The diagnosis is based on presence of at least one of the clinical features: (1) fever ≥39°C (102°F) or rise of ≥2°C (3.5°F); (2) tachycardia (heart rate >120/min, or rise of >40/min); (3) shaking chills and (4) change in systolic blood pressure (BP) (i.e. >30 mmHg rise or drop in systolic BP) within 90 min of transfusion.[16] In severe cases, the patient may develop shock with accompanying renal failure and disseminated intravascular coagulation (DIC). Isolation of the same organism from both the patient and the remainder of the bag are useful in diagnosing the transfusion-related sepsis and differentiating it from AHTRs and FNHTRs.[17] As platelets are stored at room temperature, they are more susceptible than RBCs to bacterial contamination with a greater risk. The transfusion related sepsis chances were more with random-donor platelet than with an apheresis unit. Broad spectrum antibiotics should be used for management of transfusion related sepsis with other standard care for sepsis. Screening of platelet units for bacterial contamination and adopting "diversion technique" during blood collection can decrease the risk.[18] Besides disinfectant use, bacteria may be introduced into the blood container by means of a skin core while the blood collection needle enters the skin (seen in approximately 65% of all venepunctures). In diversion technique, withdrawal of the initial 15-30 mL of whole blood from the main container might lead to reduced risk of bacterial contamination.

Non immune haemolytic reactions

Red cell haemolysis due to transfusion can also occur from several nonimmune-mediated causes (also referred as pseudohaemolysis) which may be temperature-related or mechanical; for example, improper storage temperature, improper use of blood warmer, use of hot water bath and microwave oven, using a needle with an inappropriately small bore size or employing a rapid pressure infuser, infusion of RBCs through same tubing with hypotonic solution or some pharmacologic agent. The management is same as in the AHTRs.

Transfusion associated circulatory overload

Major morbidity and mortality is associated with transfusion-associated circulatory overload.[19] Patients at greatest risk of TACO are elderly patients, infants, patients with renal failure, having hypoalbuminaemia, anaemia, congestive heart failure or fluid overload or history of plasma transfusion. Symptoms and signs include dyspnoea, orthopnoea, cyanosis, tachycardia, jugular venous distension, and pedal oedema.[20] Increased BP characterized by a widening of the pulse pressure is characteristic. It is seen in <1% of transfused patients. TACO may precipitate acute pulmonary oedema within 6 h after blood transfusion. Management is an optimization of the primary cause and mechanical ventilation, fluid restriction, diuretics.[21]

Transfusion associated dyspnoea

It is typified by respiratory distress within 24 h of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction or other known causes.[1]

Acute hypotensive transfusion reaction

This is defined as abrupt and early drop in BP with lack of other causes of hypotension. Thus, it may occur as an isolated finding, however, it responds quickly to cessation of the transfusion and supportive treatment.[22] Patients with otherwise unexplained hypotensive transfusion reactions should be given a trial of washed blood products. Bedside leucoreduction filters have been implicated more often in acute hypotensive transfusion reaction although it has also occurred with prestorage leucofilters.[23]

Metabolic and haemostatic derangement

Acute metabolic and haemostatic abnormalities may occur in association with massive transfusion. The haemostatic abnormalities may also be a part of AHTRs. The common haemostatic abnormalities seen in massive transfusion include dilutional coagulopathy, DIC, deranged liver and platelet functions. Each centre should have a massive transfusion protocol including the use of recombinant factor VIIa in place. Monitoring for coagulation status and blood component requirement may be facilitated by viscoelastic point of care test (thromboelastography).

Citrate toxicity

When large volumes of blood components containing citrate are transfused rapidly, increased plasma citrate chelates calcium ions resulting in hypocalcaemia and its symptoms. Hypocalcaemia caused by citrate overload can usually be treated by slowing the infusion rate. Calcium replacement is indicated in massively transfused patients, particularly those with severe liver disease or if symptoms of hypocalcaemia are severe.[24]

Hyperkalemia

The total extracellular potassium load, which is <0.5 mMol for fresh RBC units and only 5-7 mMol for units at expiration, rarely causes problems in the recipient because of rapid dilution, redistribution into cells, and excretion.[3] An abnormally high potassium level (>5 mmol/l or ≥1.5 moml/l net increase) within an hour of transfusion is classified as a transfusion-associated hyperkalemia.[1] Irradiation enhances the potassium leakage.

Hypokalemia

Hypokalemia is more common than the hyperkalemia after transfusion because donor red cells re- accumulate the ion intracellularly, and citrate metabolism causes further movement of potassium into the cells. Catecholamine release and aldosterone urinary loss can also trigger hypokalemia in the setting of massive transfusion. No treatment or preventive strategy is usually necessary.

Coagulopathy

Coagulopathy can be observed in massive transfusion, particularly when two blood volumes have been lost and initially replaced with red cells and fluids resulting in dilution of platelets and clotting factors. Consumption coagulopathy is an important factor in addition to dilution.

Hypothermia

It may be caused by transfusion of large volume of cold blood products. It can cause cardiac arrhythmia and also interferes with platelet function, clotting factor interaction and bleeding time.[25] Blood warmers may be used to prevent hypothermia. However, blood should never be warmed with equipment not designed

specifically for this purpose as thermal damage to blood cells and proteins may result in serious adverse reaction.

Air embolism

The incidence of air embolism has now reduced markedly with the use of plastic blood bags. Nevertheless, air can enter a central catheter while blood administration sets or blood bags are being changed or if blood in an open system is infused under pressure.[26]

Delayed reactions (occurring after 24 h or up to month/years after transfusion)

Delayed immune mediated reactions

Delayed haemolytic transfusion reactions

The incidence of delayed haemolytic transfusion reactions (DHTRs) is estimated at approximately 1 in 6000 units transfused.[27] DHTRs are seen due to reactivation of pre-existing antibodies against antigens on the transfused red cells. Symptoms may occur days to weeks after transfusion of apparently cross-matched compatible RBCs. Patients with DHTR may have unexplained anaemia or show no increment in hemoglobin following transfusion. Since the haemolysis is primarily extravascular, (implicated antibodies do not fix complement except few), acute renal failure and DIC are not manifested though haemoglobinuria may rarely occur. Sometimes there are no clinical or laboratory features of haemolysis, however, alloimmune red cell antibody is discovered. This is known as delayed serologic transfusion reaction (DSTR). Blood group antibodies associated with DHTRs/DSTRs include those of the Kidd, Duffy, Kell, and MNS systems, in order of decreasing frequency.[20] The majority of DHTRs require no treatment because red cell destruction occurs gradually as antibody synthesis increases. However, antigen negative blood may be required for a bleeding patient with low haemoglobin.

Alloimmunisation

ABO antibodies are naturally occurring antibodies (IgM); however, most other clinically significant antibodies to red cells are IgG, which is produced in response to immunisation by antigen positive red cells following transfusion, organ transplantation or foeto-maternal haemorrhage during pregnancy. It has been reported that approximately 2-3% of patients exposed to foreign red cell antigens will form alloantibodies to one or more of these antigens. As many as 30-40% of sickle cell anemia patients and 9% of thalassemia major patients have been reported to have alloantibodies.[28] An acute life-threatening anaemia (hyper haemolysis syndrome) can occur in some sickle cell and thalassemia patients when they are multiply transfused.[29] In the absence of an antigenic stimulus, antibody production decreases and eventually disappears in most cases over the course of time.[30] Patients with history of pregnancy or non-leukocyte depleted transfusion produce alloantibodies against HLA, which contribute to the highest proportion of alloimmune-mediated platelet transfusion refractoriness. A less-than-expected increase in platelet count occurs in about 20-70% of multi transfused thrombocytopenic patients. The trial to reduce alloimmunisation to platelets study group found that leucocyte reduction, not the number of donor exposures, was significant in modifying the rate of sensitisation.[31] Transfusion with HLA-and/or HPA-matched platelets is required to reduce the risk of bleeding in refractory patients.[32]

Transfusion associated immunomodulation

The down-regulation of recipient's cellular immune response caused by transfusion of allogeneic blood has traditionally been defined as Transfusion associated immunomodulation (TRIM).[33] The detrimental clinical impacts of TRIM are increased chances of post-operative infections and cancer recurrence and possibly a transfusion-related multiple organ dysfunction syndrome.[34] TRIM is presumably mediated by allogeneic leucocytes or their soluble products. One of the plausible mechanisms put forward is immune deviation towards T-helper lymphocytes type 2 cytokine charactericed by secretion of interleukin (IL-4), IL-5, IL-10 cytokines with reduced secretion of T-helper lymphocytes type 1 cytokines namely IL-2, IL-12, and interferon-γ. Use of autologous blood or prestorage leucofiltered blood can mitigate the adverse effects of TRIM.[35]

Transfusion-associated graft versus host disease

Transfusion-associated graft versus host disease (TA-GVHD) is a clinical syndrome characterized by fever, maculopapular rash progressing to haemorrhagic bullae, enterocolitis with watery diarrhoea, elevated liver function tests, pancytopenia and findings of characteristic histological appearances on biopsy that typically begin 8-10 days after transfusion.[36] In TA-GVHD, viable transfused T-lymphocytes mount an immunologic attack against the immunocompromised transfusion recipient incapable of rejecting the immunocompetent cells. TA-GVHD can also occur after transfusion from a blood related donor who is homozygous for an HLA haplotype to a heterozygous

recipient (one-way haplotype match).[37] HLA typing and other molecular studies can detect chimerism and thus aid in the diagnosis. Although rare in occurrence, it has a mortality of 90%. Therefore, emphasis is placed on prevention of TA-GVHD by irradiation of all cellular blood components (RBCs, platelets, and granulocytes), especially in patients at risk of TA-GVHD.[38]

Posttransfusion purpura

Posttransfusion purpura (PTP) is a relatively uncommon complication of transfusion with female preponderance. It occurs between 1 and 24 days after transfusion with a mean of 9 days.[39] Patients typically present with purpuric rash and thrombocytopenia (platelet counts often <10,000/μL) resulting in bleeding from mucous membranes and the gastrointestinal and urinary tracts. The primary cause of mortality is intracranial haemorrhage. PTP has most commonly been associated with the transfusion of RBCs or whole blood; however, it has also been associated with the transfusion of platelets and plasma. Antibodies against HPA-1a are responsible in most cases although, antibodies to HPA-1b, other platelet antigens, and HLA antigens are also implicated. The current treatment of choice for PTP is high dose intravenous immune globulin.[40] Platelet transfusions are usually ineffective in raising the platelet counts in these patients.

Delayed non-immune mediated reactions

Iron overload

Patients who are chronically transfused for diseases such as thalassemia, sickle cell disease, and other chronic anaemia are at the greatest risk for iron overload. A unit of RBCs contains approximately 250 mg of iron. As red cells are destroyed, the majority of the released iron cannot be excreted and is stored in the body as haemosiderin and ferritin. Transferrin becomes saturated after the administration of 10-15 units of RBCs to a non-bleeding patient and iron accumulates in the reticuloendothelial system, liver, heart, spleen, and endocrine organs causing tissue damage leading to heart failure, liver failure, diabetes and hypothyroidism.[3]

Adverse transfusion reactions during surgery under anaesthesia

It may vary from mild anaphylaxis to any severe life threating conditions as described in this review. It may be easy to identify adverse reactions with proper heamovigilance and monitoring in awake patients timely. However, it is very difficult to identify adverse transfusions reactions under anaesthesia and in situations where patients are unable to report symptoms (e.g. infants, children, unconscious). In these situations, the classical presentation of adverse transfusions reactions is usually masked. However, under anaesthesia one can suspect it whenever patient develops various type of arrhythmias, tachycardia and hypotension, localised or systemic cutaneous reactions, increased airway resistance due to laryngospasm or bronchospasm and uncontrolled bleeding immediately following blood transfusion. The haemoglobinuria or diffuse bleeding (DIC) may be the only signs of acute intravascular red cell haemolysis with possibility of other causes to be ruled out. It is advised to always record the following information on the patient's notes: Type of transfusion reaction suspected, length of time after the start of transfusion that the reaction occurred, volume, type and pack numbers of the blood products transfused. By applying the International Society of Blood Transfusion criteria of adverse transfusion reactions, one can identify it during anaesthesia and surgery.[41]

SUMMARY

Acute transfusion reactions are responsible for causing most serious adverse reactions or events. Awareness about various clinical features of acute transfusion reactions with an ability to assess the serious reactions on time can lead to a better prognosis. Observation and monitoring are required throughout the transfusion episode, more so for with in first 15 min. There should be a standard operating procedure containing the details for documentation, reporting, evaluation, and follow-up of all adverse reactions. Evidence based approach of Restrictive strategy" or "Conservative approach" of blood transfusion to reduce the number of unwanted transfusions has made a gross change in current clinical practice.

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