Complications of blood transfusion

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The serious hazards of transfusion (SHOT) scheme has collected data on significant adverse events resulting from transfusion of blood components from volunteer organizations since 1996. However, after the implementation of the European Union Directive on Blood Safety and Quality in 2005, it is now a requirement that all 'Blood Establishments and Hospital Blood Banks report to the Secretary of State for Health all serious adverse reactions attributable to the safety or quality of blood.'[1]

In 2004, 3.4 million blood components were issued in the UK and 539 events were voluntarily reported to SHOT. This represents an increase of 19% over 2003. Data collected as reporting became compulsory are not yet available (www.transfusionguidelines.org.uk).[1]

Serious complications of blood transfusion are outlined in Table 1. Although immunologically mediated reactions to transfusion products are potentially serious, anaesthetists are most likely to encounter those relating to massive blood transfusion and transfusion-related acute lung injury (TRALI). These adverse events are of most relevance to our profession and will be discussed first.

Table 1 Complications of blood transfusion

Early
  Haemolytic reactions
    Immediate
    Delayed
  Non-haemolytic febrile reactions
  Allergic reactions to proteins, IgA
  Transfusion-related acute lung injury
  Reactions secondary to bacterial contamination
  Circulatory overload
  Air embolism
  Thrombophlebitis
  Hyperkalaemia
  Citrate toxicity
  Hypothermia
  Clotting abnormalities (after massive transfusion)
Late
  Transmission of infection
    Viral (hepatitis A, B, C, HIV, CMV)
    Bacterial (*Treponeum pallidum, Salmonella*)
    Parasites (malaria, toxoplasma)
  Graft-*vs*-host disease
  Iron overload (after chronic transfusions)
  Immune sensitization (Rhesus D antigen)

Massive transfusion

A massive blood transfusion is defined as the replacement of a patient's total blood volume in <24 h.[2] The abnormalities which result include effects upon coagulation status, serum biochemistry, acid–base balance and temperature homeostasis.

Coagulation

A massive transfusion of red blood cells (RBCs) may lead to a dilutional coagulopathy, as plasma-reduced RBCs contain neither coagulation factors nor platelets. Secondly, haemorrhage, as a consequence of delayed or inadequate perfusion, can result in disseminated intravascular coagulation. This causes consumption of platelets and coagulation factors and may account for the numerical distortion of clotting studies appearing out of proportion to the volume of blood transfused. Aggressive, expectant replacement of clotting factors with fresh frozen plasma (FFP), platelets and cryoprecipitate transfusions are required to prevent this coagulopathy becoming severe enough to make haemorrhage worse.[2]

Biochemistry

Hypocalcaemia

RBCs in additive solution contain only traces of citrate, however, FFP and platelets contain much higher concentrations. Citrate binds calcium, thus lowering the ionized plasma calcium concentration. This is usually prevented by rapid hepatic metabolism unless the patient is hypothermic.[2] Calcium is an important co-factor, especially in coagulation, and has a key role in mediating the contractility of myocardial, skeletal and smooth muscles. Hypocalcaemia results in hypotension, small pulse pressure, flat ST-segments and prolonged QT intervals on the ECG. If there is clinical, biochemical or ECG evidence of hypocalcaemia, it should be treated with slow i.v. injection of calcium gluconate 10% (5 ml).[2]

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Hyperkalaemia

The potassium concentration of blood increases during storage, by as much as 5–10 mmol u^{-1}. After transfusion, the RBC membrane Na$^+$–K$^+$ ATPase pumping mechanism is re-established and cellular potassium reuptake occurs rapidly. Hyperkalaemia rarely occurs during massive transfusions unless the patient is also hypothermic and acidotic.[2]

Acid–base abnormalities

Each unit of RBCs contains 1–2 mmol of acid. This is generated from the citric acid of the anticoagulant and from the lactic acid produced during storage; metabolism of this acid is usually very rapid. Citrate undergoes hepatic metabolism to bicarbonate and during a massive transfusion a metabolic alkalosis may occur. A patient's acid–base status is also dependent on tissue perfusion, and acidosis often improves after adequate fluid resuscitation.[2]

Hypothermia

RBCs are stored at 4°C. Rapid transfusion at this temperature will quickly lower the recipient's core temperature and further impair haemostasis. Hypothermia reduces the metabolism of citrate and lactate and increases the likelihood of hypocalcaemia, metabolic acidosis and cardiac arrhythmias. A decrease in core temperature shifts the oxyhaemoglobin dissociation curve to the left, reducing tissue oxygen delivery at a time when it should be optimized. This reduction in temperature can be minimized by warming all i.v. fluids and by the use of forced air convection warming blankets to reduce radiant heat loss.[2]

Transfusion-related acute lung injury

TRALI is the most common cause of major morbidity and death after transfusion. It presents as an acute respiratory distress syndrome (ARDS) either during or within 6 h of transfusion.[3]

Clinical features

Hypoxaemia, dyspnoea, cyanosis, fever, tachycardia and hypotension result from non-cardiogenic pulmonary oedema. Radiographic appearance is of bilateral pulmonary infiltration, characteristic of pulmonary oedema. It is important to differentiate TRALI from other causes of ARDS such as circulatory overload or myocardial or valvular heart disease. Invasive monitoring in TRALI demonstrates normal intracardiac pressures.[3]

Pathogenesis

Two different mechanisms for the pathogenesis of TRALI have been identified: immune (antibody-mediated) and non-immune. Immune TRALI results from the presence of leucocyte antibodies in the plasma of donor blood directed against human leucocyte antigens (HLA) and human neutrophil alloantigens (HNA) in the recipient. Antibodies present in the recipient only rarely cause TRALI. In up to 40% of patients, leucocyte antibodies cannot be detected in either donor or recipient. In these cases it is possible that reactive lipid products released from the membranes of the donor blood cells act as the trigger. This is known as non-immune TRALI.[3]

The target cell in both forms of TRALI is the neutrophil granulocyte. On activation of their acute phase cycle, these cells migrate to the lungs where they become trapped within the pulmonary microvasculature. Oxygen free radicals and other proteolytic enzymes are then released which destroy the endothelial cells of the lung capillaries. A pulmonary capillary leak syndrome develops with the exudation of fluid and protein into the alveoli resulting in pulmonary oedema. The majority of reactions are severe, and often life threatening; 70% require mechanical ventilation and 6–9% are fatal. A definitive diagnosis requires antibody detection. The mortality in non-immune TRALI is lower, and the syndrome is encountered predominantly in critically ill patients.[3]

Incidence

The exact incidence is unknown. Immune TRALI is reported to occur with an overall frequency of 1 in 5000 transfused units and non-immune TRALI with a frequency of 1 in 1100.[3] The 2004, SHOT report describes 13 reactions as follows: 6 to FFP, 4 to platelets, 2 to packed cells and 1 to whole blood. The preponderance of reactions with FFP and platelets is thought to result from their 'high plasma component', in comparison with packed cells and cryoprecipitate, which have a 'low plasma component'. There is a 10-fold plasma difference between the two types of transfusion product; 300 ml compared with 30 ml.[1] Measures taken to reduce the risk of TRALI include sourcing plasma for FFP and platelet suspension solely from male donors; HLA antibodies are more common in multiparous women as a result of transplacental passage during pregnancy. The incidence of immune TRALI has also been significantly reduced by the leucodepletion of transfused blood (www.blood.co.uk).

Haemolytic transfusion reactions

The most serious complications of blood transfusion result from interactions between antibodies in the recipient's plasma and surface antigens on donor RBCs. Although more than 250 RBC group antigens have been described, they differ in their potential for causing immunization. The ABO and Rhesus D groups account for the majority of reactions of clinical significance.

Blood group antibodies are either naturally occurring or immune in origin. Naturally occurring antibodies are present in the plasma of individuals who lack the corresponding antigens. The most important are anti-A and anti-B, and they are usually of the IgM class. Immune antibodies develop after a subject's

exposure to RBCs expressing antigens which they lack. This results from previous blood transfusions or transplacental passage during pregnancy. They are commonly IgG in origin.[4]

Haemolytic transfusion reactions may either be immediate or delayed.

Immediate reactions

Incompatibility between donor RBC antigens and recipient plasma antibodies produces an antigen–antibody complex causing complement fixation, intravascular haemolysis and ultimately destruction of the transfused blood. The severity of the reaction depends upon the recipient's antibody titre. Severe reactions are most often the result of ABO incompatibility and can be precipitated by transfused volumes of only a few millilitres.[4][5]

Symptoms manifest soon after starting the transfusion. In the conscious patient, they include head, chest and flank pain, fever, chills, flushing, rigors, nausea and vomiting, urticaria, dyspnoea and hypotension. In anaesthetized patients, these features may be masked and the first signs may be hypotension and the features of increased blood destruction; namely, haemoglobinuria and disseminated intravascular coagulation.[4][5]

These reactions constitute medical emergencies. Consequently, management of the reaction precedes investigation into its cause. The transfusion should be stopped immediately, and attention directed towards cardiac and respiratory support and the maintenance of adequate renal perfusion. Microvascular thrombosis and deposition of haemoglobin in the distal renal tubule can result in acute renal failure. The extent of precipitation is inversely related to urine flow. I.V. fluids, vasopressors and diuretics should be given to maintain renal perfusion pressure, and to produce a diuresis. If acute renal failure develops, haemofiltration should be considered.[4][5]

Haemolytic transfusion reactions should be investigated as a matter of urgency. The transfusion products administered should be meticulously documented and returned to the laboratory together with a post-transfusion blood sample. Repeat blood group analysis and compatibility testing will be performed. In cases of true haemolytic transfusion reaction, the direct antiglobulin test (Coombs' test) will be positive, because donor RBCs are coated with recipient antibody. Haemoglobinaemia, haemoglobinuria and a increase in both serum unconjugated bilirubin and lactate dehydrogenase concentrations are useful in confirming the diagnosis.[4][5]

Delayed reactions

The donor RBC antigen–plasma antibody interactions responsible for this subset of transfusion reaction more commonly result from incompatibility with minor blood groups such as Rhesus and Kidd. On pre-transfusion antibody screening, these patients commonly test negative because their antibody titres are too low to be detected. However, on further exposure to the antigen,

their antibody production is greatly increased; this is known as an anamnestic response. Antibody–antigen interactions of this nature do not activate the complement system, so extravascular rather than intravascular haemolysis occurs. The RBCs become coated with IgG and are then removed by the reticuloendothelial system.[4][5]

The presence of a low concentration of antibody means that RBC destruction is delayed. Transfused cells are destroyed after a variable period of between 7 and 21 days. Indicators of a delayed haemolytic transfusion reaction are an unexpected reduction in haematocrit after transfusion, jaundice (unconjugated hyperbilirubinaemia) and a positive direct antiglobulin test.[5]

Delayed transfusion reactions are difficult to prevent as very low titres of antibody in recipient's plasma are not easily detected. Subsequent antibody production may complicate later transfusions.

Non-haemolytic febrile reactions

These reactions are very common and are usually not life threatening. Reactions result from donor leucocyte antigens reacting to antibodies present in the recipient's plasma. These antibodies react with the leucocytes to form a leucocyte antigen–antibody complex that binds complement and results in the release of endogenous pyrogens—IL-1, IL-6 and TNFα. Non-haemolytic febrile reactions can also occur after platelet transfusions and are not caused by antibodies but by cytokines derived from contaminating leucocytes that have accumulated in the bag during storage.[4] Since the introduction of universal leucodepletion in 1999, a noticeable reduction in febrile reactions to both RBCs and platelets has been observed.

Symptoms of non-haemolytic febrile reactions include fever, chills, headache, myalgia and general malaise. Rarely, they may progress to hypotension, vomiting and respiratory distress. Onset is during, or several hours after, transfusion and the severity of the reaction is dependent upon leucocyte-load and the rate of transfusion. Fever is a feature of both non-haemolytic febrile and haemolytic transfusion reactions. Distinction may be drawn between these two diagnoses by performing a direct antiglobulin test. This will be negative with febrile reactions as there will be no attachment of plasma antibody to donor RBCs.[4][5]

Controversy exists in the current literature on whether the transfusion should be discontinued; however, there is consensus that the rate of transfusion should be reduced. Anti-pyretics such as acetaminophen should be administered.

Allergic reactions

Allergic reactions are common and usually mild. The majority are because of the presence of foreign proteins in donor plasma and are IgE-mediated. Pruritus and urticaria, with or without fever, are the most common features. The transfusion should be stopped and anti-histamines administered. If symptoms resolve in less than 30 min and there is no cardiovascular

instability, the transfusion may be restarted. If the symptoms recur then administration of that particular unit of blood should be abandoned.[5]

Anaphylactic reactions are rare after transfusions. They occur most often in patients in whom a hereditary IgA deficiency, and pre-existing anti-IgA antibodies, predisposes to an antibody–antigen interaction and subsequent anaphylaxis. This reaction occurs immediately after commencement of transfusion and is not dose-related. Clinical features include urticaria, dyspnoea, bronchospasm, laryngeal oedema and cardiovascular collapse. Treatment is the same as for anaphylaxis from other causes, with i.v. fluid resuscitation, epinephrine administration to re-establish vasomotor tone and reverse bronchospasm, antihistamines, corticosteroids and respiratory support. If subsequent transfusions are required in such patients, washed RBCs should be used (residual plasma and therefore IgA removed).[5]

Transfusion-related infections

Bacterial

Bacterial contamination of blood components is an infrequent complication of transfusion. However, if it does occur, the potential for fulminant sepsis in the recipient is associated with high mortality. It can result from contamination during venepuncture or if an asymptomatic donor is bacteraemic at the time of donation. Symptoms occur during or shortly after transfusion of the contaminated unit and include high fever, rigors, erythema and cardiovascular collapse.[6]

RBCs are stored at 4°C. This makes contamination with Gram-negative bacteria such as *Yersinia enterocolitica* and *Pseudomonas* species more likely as they proliferate rapidly at this temperature. Gram-positive bacteria such as *Staphylococcus epidermidis, Staphylococcus aureus* and *Bacillus* species proliferate more readily at room temperature and so are more commonly seen as platelet contaminants. There are no screening tests currently available for detection of bacterial contamination; therefore, visual inspection of the bag before transfusion is important. Contaminated bags may seem unusually dark in colour or contain gas bubbles. Diagnosis rests with culture of the same organism from both the patient and the implicated blood component.[6]

Viral

The incidence of transfusion-related viral infection has greatly reduced since the mid-1980s when pre-donation questionnaires to identify groups with high-risk behaviour were implemented. There have also been improvements in pre-transfusion testing of donated blood. Currently, donor blood is screened for hepatitis B, hepatitis C, HIV 1 and 2, human T cell lymphotrophic virus, syphilis and cytomegalovirus. However, disease transmission may occur in the 'window period', that is, the time after infection when the donor is infectious but screening tests are negative.[4]

Table 2 Current risk of transfusion-related infection after a unit of screened blood in the UK

Infection	Estimated risk per unit of transfused blood
Hepatitis A	Negligible
Hepatitis B	1 in 100 000
Hepatitis C	<1 in 1 000 000
HIV 1 and 2	<1 in 4 000 000

Table 2 shows the current risk of transfusion-related infection from a unit of screened blood in the UK.

Prion

Variant Creutzfeldt-Jakob disease (vCJD) is a human prion disease caused by infection with the bovine spongiform encephalopathy (BSE) agent. There is a theoretical risk that vCJD might be transmitted through blood transfusion. Therefore, the National Blood Service has undertaken precautionary measures. These include leucodepletion of blood, obtaining plasma for fractionation from countries other than the UK and exclusion of donors who themselves received transfusions before 1980. At present, no treatment or test for vCJD exists.[4]

Transfusion-associated graft-*vs*-host disease

Transfusion-associated graft-*vs*-host disease (GvHD) is a very rare complication of blood transfusion; there are no identifiable cases in the most recent SHOT report. This reduction in incidence has resulted from the implementation of universal leucodepletion. GvHD can complicate allogenic bone marrow transplants, but in those who are immunocompromised, it can occur after simple blood transfusion. Ninety per cent of cases are fatal. Donor-derived immune cells, particularly T lymphocytes, mount an immune response against host tissue. Clinical features include a maculopapular rash (typically affecting the face, palms and soles), abdominal pain, diarrhoea and abnormal liver function tests. Destruction of bone marrow stem cells by donor T lymphocytes causes a pancytopenia. Prevention is by irradiation of blood products which inactivates any donor lymphocytes.[4][5]

Immunomodulation

The potential to modulate the immune system of transfusion recipients remains an exciting but controversial area of transfusion medicine. The prolonged survival of renal allografts in patients who have received pre-transplantation blood transfusions is evidence for this effect. Transfusion-related immune suppression is manifest as an increased risk of postoperative infections, increased tumour recurrence after surgical resection, activation of latent viral infection, improvement in immune inflammatory disease and prevention of recurrent miscarriage. These effects are thought to be initiated by donor leucocytes and are related to the Class I and Class II HLA antigens which they express. It is possible that the aetiology of

immunomodulation is multifactorial as laboratory studies have shown a reduction in natural killer cell activity, IL-2 production, CD4/CD8 ratios and macrophage function.[7]

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Please see multiple choice questions 9–11.