THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Delaney M, Wendel S, Bercovitz RS, et al, for the Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* 2016; published online April 12. http://dx.doi.org/10.1016/S0140-6736(15)01313-6.

Prevention, Diagnosis, and Treatment of Transfusion Reactions:

Evidence-Based Review & Clinical Guideline

APPENDIX, WEB – ELECTRONIC

This appendix provides single page reference sheets for each transfusion reaction diagnostic category for use at the bedside. Evidence-based recommendations using the Chest grading system are included.[1]

Table of Contents

ACUTE HAEMOLYTIC TRANSFUSION REACTION (AHTR), IMMUNE

Incidence

- 2.2 – 7.9 per 100,000 units
- 2nd leading cause of death reported to the FDA
- Fatality rate of 1 per 1.8 million units

Blood products

- Red Blood Cells (RBCs) and Whole Blood
- Platelets, Apheresis

		Grade
Management	RBC and/or Plasma Exchange	2C
	Complement inhibitors	2C
	Intravenous Immune Globulin (IVIG)	2C
Prevention	Procedures to ensure accurate patient identification	1A
	ABO Confirmation (i.e. Check Type, Two Sample Policy)	1A
	Technology for patient identification (barcode, RFID)	1A

Clinical findings & diagnosis

Acute haemolytic transfusion reactions (AHTR) to RBC containing products occur during or within 24 hours of transfusion of antigen positive RBCs to a patient with pre-existing RBC antibodies (either ABO or antibodies due to previous sensitization). Plasma-containing blood components (plasma, apheresis platelets, IVIG) can also cause AHTR when the plasma contains sufficient antibody directed against the patient's RBC antigens. The antibody-antigen interaction results in complement activation, phagocyte activation and production of proinflammatory mediators leading to rapid intravascular haemolysis and opsonization as well as generation of anaphylatoxins. Severe extravascular reactions can occur as well.

The most common clinical presentations include sudden onset of fever and chills (80%), facial flushing, pain (flanks, back, abdomen, groin, chest, and infusion site), hypotension, dyspnea, and disseminated intravascular coagulation (DIC). Fever and chills may be the only manifestations. Other symptoms include acute renal failure due to acute tubular necrosis, shock and death. Based on SHOT data, death occurred in 7% of cases and major morbidity in 22%. In an unconscious/sedated patient, the initial manifestation may be uncontrollable bleeding as a result of DIC. Gross haemoglobinemia and haemoglobinuria are present. A diagnosis of AHTR includes laboratory evidence of haemolysis such as elevated lactate dehydrogenase (LD) and serum (indirect) bilirubin, decreased haptoglobin accompanied by a less than expected rise in post-transfusion haemoglobin concentration. Blood bank work-up includes evaluation for clerical error, repeat serologic crossmatch, evaluation of a post-transfusion specimen for gross haemolysis, and performance of ABO/Rh typing and direct antiglobin (Coombs) test (DAT). Serologic incompatibility confirms the diagnosis. Non-immune causes of haemolysis must be excluded (refer to Acute Haemolytic Transfusion Reaction, Non-Immune).

Management

Stop transfusion immediately and confirm patient identity (to ensure that the correct patient received the correct blood product); the severity of the reaction and mortality depend, in part, on the amount of incompatible blood transfused. Maintain large-bore IV access and monitor the patient with careful observation, in the ICU setting if need be. In severe reactions, immediate intervention with fluid resuscitation; cardiovascular, renal and/or respiratory support; and blood component therapy for DIC with bleeding can be lifesaving and significantly reduce morbidity. No evidence exists for any specific intervention in the treatment of an AHTR, although case reports/series highlight the benefit of treatment with RBC/plasma exchange, IVIG and complement inhibitor medications. Notification of blood bank and return of any unused blood products are essential to minimize risk of transfusion of additional incompatible units and prevent occurrence of a second "wrong" blood incident in another patient.

Prevention

Patient misidentification remains the main cause of ABO-incompatible RBC transfusions. Systems-based practices and comprehensive training to ensure proper patient identification at critical steps in the transfusion process (wristband application, specimen collection and transfusion administration with 2-person check), provide ABO confirmation prior to transfusion, and standardize data transmission (communication including hand-off) between health care personnel must be adopted. Deployment of technologies to improve transfusion safety (such as barrier systems, bar codes and RFID) should be utilized where available.

References [2-14]

ACUTE HAEMOLYTIC TRANSFUSION REACTION (AHTR), NON-IMMUNE

Incidence	**Blood products**
• Rare, but likely under reported	• Red Blood Cells (RBCs) and Whole Blood

		Grade
Management	No specific management; supportive care	N/A
Prevention	Adherence to all guidelines on appropriate RBC transport, handling and infusion	1A

Clinical findings & diagnosis

There can be many causes of non-immune haemolytic transfusion reactions. Any maneuver that lyses RBCs before they are infused can cause this reaction. Although this reaction is rare (but likely under reported), some of the more common causes include: infusing RBCs with an incompatible solution (such as D5W) or other medications; administering RBCs though a non-validated or malfunctioning blood warmer; placing RBCs on unapproved heat sources, in microwaves or in unapproved or malfunctioning high pressure administration devices; and administering RBCs at a high rate through a small gauge syringe or narrow tubing.

There are no patient risk factors associated with this type of reaction. Historically, patients with mechanical heart valves were at risk of shearing RBCs (presumably both autologous and allogeneic RBCs), however the term non-immune AHTR specifically applies to the destruction of transfused RBCs by factors other than an antibody (immune).

Often patients do not manifest any signs or symptoms when they are transfused with a unit containing lysed RBCs. However, some patients may demonstrate some degree of haemodynamic instability, transient hypertension from the free haemoglobin, renal insufficiency/failure, haemoglobinemia and/or haemoglobinuria, and cardiac arrhythmia from hyperkalemia. Rarely, DIC can be caused by the presence of intravascular RBC stroma.

The diagnosis of non-immune AHTR is typically one of exclusion. The main differential diagnosis includes immune causes of haemolysis and non-immune causes such as sepsis or other elements in the patient's underlying disease like a hyperhaemolysis crisis in a patient with sickle cell disease. If non-immune haemolysis is suspected after elimination of other more common causes of haemolysis, a careful review of the handling, transport and especially the administration of the RBC unit are necessary. The investigation must include discussion with everyone involved in handling the unit once it had been issued from the blood bank to ensure that all protocols had been followed properly. Sometimes, if an incompatible fluid (i.e., anything other than normal saline) had been co-administered with the RBC unit, the fluid bag will remain connected to the RBC unit through a "Y" connection; therefore examination of the unit and associated tubing/solutions can quickly reveal the cause of the haemolysis.

Management

For all transfusion reactions, stop the transfusion, provide supportive treatment according to the patient's signs and symptoms addressing vital cardiac, respiratory and renal functions; send the appropriate report, remaining RBC unit(s) with associated tubing, and post-transfusion patient sample to the blood bank. As the amount of free haemoglobin and RBC stroma from the lysed RBCs is finite, the signs and symptoms are expected to be self-limiting and proportionate to the volume of transfusion. Intravenous fluid administration may aid in supporting renal function if the haemoglobin rich red cell lysate is impacting renal function.

Prevention

Ensuring that all individuals who transport, handle and infuse blood products are familiar with, and follow, their hospital's policy on dealing with blood products. Typically only normal saline is compatible with blood products, however if a question arises as to whether a medication or another fluid is compatible with a blood product, call your blood bank before co-administering it with the blood product.

References [12, 14-17]

ALLERGIC TRANSFUSION REACTION

Incidence

- Overall: 112.2 per 100,000 units
- RBCs: 53.6 per 100,000 units
- Platelets: 302 per 100,000 units
- Plasma: 105.7 per 100,000 units
- Cryoprecipitate: 4.8 per 100,000 units
- Granulocytes: Unknown

Blood Products

- Plasma, FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid plasma
- Red Blood Cells (RBCs) and Whole Blood
- Platelets (Apheresis and Whole Blood Derived Pooled)
- Granulocytes

		Grade
Management	Antihistamine (H_1 antagonists)	1A
	Glucocorticoids	1C
Prevention	Supernatant removal or wash	1C
	Platelet stored in Platelet Additive Solution	1C
	Solvent/Detergent Treated Plasma	1C
	Premedication with antihistamine (no history of reaction or history mild reaction)	Not indicated, 2C

Clinical findings & diagnosis

Diagnosis is based on common clinical findings of urticaria, pruritus, erythematous or maculopapular rash, flushing, angioedema, bronchospasm/respiratory distress, and/or hypotension. These signs and symptoms may occur up to four hours after cessation of transfusion, but usually manifest during transfusion. Most allergic reactions are mild, however, a wide spectrum of severity of symptoms is seen with more severe reactions usually involving dyspnea and hypotension. A life-threatening, generalized or systemic reaction is defined as anaphylaxis (refer to Anaphylactic Transfusion Reaction). Fever is not part of the allergic response. Other acute transfusion reactions with similar presentations such as TACO, TRALI, hypotensive and septic transfusion reactions should be excluded.

Management

As per all acute transfusion reactions, infusion of the blood component must be immediately stopped with prompt clinical assessment of the patient, confirmation of patient identity, examination of the transfused component and notification of the blood bank. Antihistamines such as diphenhydramine (25 – 50 mg, PO or IV) may bring symptomatic relief with mild reactions. A combination of H_1 and H_2 antagonists may also be used. In more severe reactions, methylprednisone (125 mg IV) or prednisone (50 mg PO) may be needed. Supportive measures should be taken as necessary. Anaphylaxis requires epinephrine (see Anaphylactic Transfusion Reaction). When reactions are limited to cutaneous symptoms, a transfusion may be re-started once the symptoms have resolved with treatment; a reduced transfusion rate is recommended and transfusion must be stopped if any new symptoms appear.

Prevention

Removal of plasma proteins reduces the incidence of allergic reactions. Washing to remove plasma from red blood cell and platelet units is the most effective method to reduce the risk of a moderate to severe allergic reaction, however, this technique reduces the quality of the component and shortens the component shelf life. Volume reduction, or supernatant removal from platelet units reduces the risk of an allergic reaction, and brings a lesser decrease in component quality and longevity, and therefore is preferred as an initial preventative measure. Platelets stored in additive solutions have reduced plasma content and are associated with a lower rate of allergic reactions. Recurrent allergic transfusion reactions in patients treated with plasma exchange may be reduced by the use of solvent-detergent (SD) treated products. In patients with no history of reaction or only previous mild allergic transfusion reactions, pre-medication with antihistamines and/or glucocorticoids is not indicated.

References [3, 18-25]

ANAPHYLACTIC TRANSFUSION REACTION

Incidence

- 8 per 100,000 units

Blood products

- Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid)
- Red Blood Cells (RBCs) and Whole Blood
- Platelets (Apheresis and Whole Blood Derived Pooled)
- Granulocytes

		Grade
Management	Epinephrine/Adrenaline	1A
	High-flow supplemental oxygen, rapid fluid administration with crystalloid solution (0.9% saline)	1C
	Second line medications: Antihistamine (H_1 and H_2 antihistamines), Bronchodilator therapy, Glucocorticoids	1C
Prevention	Discuss with allergist/immunologist and transfusion physician	1C
	Administer transfusion in a clinical area with direct observation & resuscitation capabilities	2C
	Transfuse with plasma-reduced (washed) cellular components	2C
	Premedication with antihistamine	2C

Clinical findings & diagnosis

Diagnosis is based on clinical findings and temporal association with (during or within 4 hours) transfusion. Anaphylaxis is highly likely if sudden symptoms or signs occur in two or more systems:

- Skin or mucosal: rash, pruritus, urticaria (hives), angioedema, erythema, edema
- Respiratory : laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing/bronchospasm, hypoxemia)
- Cardiovascular/CNS: hypotension, syncope, collapse, incontinence
- Gastrointestinal: abdominal pain, vomiting

Mechanisms include activation of mast cells and basophil granulocytes with mediator release.

Management

Anaphylaxis requires prompt intramuscular (mid-anterolateral thigh) administration of epinephrine/adrenaline 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, to a maximum of 0.5 mg (adult) or 0.3 mg (child). Treatment should be guided by expert medical assessment and appropriate specialist support. Supportive measures include high-flow supplemental oxygen, rapid fluid administration with 500–1000 mL crystalloid solution (0.9% normal saline), and second line medications: H_1- Antihistamine administration [e.g. Chlorpheniramine 10 mg (adult), 2.5–5 mg (child) or Diphenhydramine 25–50 mg (adult), 1 mg/kg, maximum 50 mg (child)], Bronchodilator therapy [(β_2-adrenergic agonist; e.g. Salbutamol (albuterol) solution 2.5 mg/3 mL or 5 mg/3 mL (adult), 2.5 mg/3mL (child) given by nebulizer and face mask], Glucocorticoid for iv administration [e.g. Hydrocortisone 200 mg (adult) maximum 100 mg (child) or Methylprednisolone 50–100 mg (adult), 1 mg/kg, maximum 50 mg (child)] , and H_2-antihistamine [e.g. Ranitidine 50 mg (adult) or 1 mg/kg, maximum 50 mg (child)].

Prevention

Patients should be counselled about their diagnosis. The care team should be prepared for recurrent reactions; transfusions must be directly monitored. Minimising the plasma content by removing excess supernatant (washing) or using platelets stored in additive solutions should reduce the risk or using prothrombin complex concentrates in place of plasma products may be appropriate. Laboratory investigations include exclusion of serum protein deficiency (e.g., IgA, haptoglobin), and other allergies (e.g., drugs, latex). In the case of IgA deficiency and previous allergic transfusion reaction, use of IgA-deficient blood donor or washed components may be undertaken, however the clinical evidence is debated. Evidence for efficacy of premedication with antihistamines is low, but risk of using premedication is also low.

References [3, 18-20, 22, 26-29]

CITRATE TOXICITY

Incidence	**Blood products**
• Unknown	• Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid) • Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled)

		Grade
Management	Calcium administration	1A
Prevention	Calcium administration	1B

Clinical findings & diagnosis

All blood products contain some amount of sodium citrate, which is used to bind calcium and prevent coagulation during storage. Each RBC unit contains approximately 3 grams of citrate.

The metabolic pathways that breakdown citrate include the Krebs cycle, a transaminase reaction with glutamate, as well as cleavage. These pathways are found in the organs that receive the highest cardiac output; such as liver, kidney and skeletal muscle. The liver's ability to metabolize citrate is diminished with liver disease, hypothermia, and in infants, whose metabolism of citrate is lower than that of adults.

It is estimated that the 3 grams of citrate contained in each unit can be metabolized by a healthy adult liver every 5 minutes. When the metabolic machinery's ability to break down the citrate is exceeded, ionised calcium levels in the blood can drop (hypocalcemia). Citrate toxicity, or transfusion-related hypocalcemia, is most commonly seen in the setting of massive transfusion (though can present after transfusion of a few RBC units), liver transplantation, and in therapeutic apheresis, when sodium citrate is used as the anticoagulant during the apheresis procedure. Hypocalcemia from citrate toxicity causes alterations of cardiac depolarisation (prolonged QT on EKG) and blunting of left ventricular response. It also can cause alkalosis, hypotension, mouth bitterness, shivering, nausea, perioral and peripheral paresthesia, muscle fasciculations, and carpopedal spasm, due to perturbation of calcium at the nerve membrane. The diagnosis of hypocalcemia is based on clinical signs or symptoms, or by routine measurement of ionised calcium (iCa) levels. Total serum calcium is not a useful measure of hypocalcemia because it does not reflect the most readily bioavailable portion of calcium in the body.

Management

Management of hypocalcemia is achieved by administration of supplemental calcium, preferably with regular monitoring of iCa levels. The calcium formulation employed is usually calcium gluconate or calcium chloride; note that 1 gram of chloride provides 4 times as much calcium as 1 gram of gluconate. In the setting of massive transfusion, the management of citrate toxicity with calcium electrolyte normalization must occur simultaneously with the management of transfusion-related hypothermia, hyperkalemia, coagulopathy and acidosis. A typical calcium gluconate bolus dose is approximately 20 mg/kg for signs and symptoms of hypocalcemia, or for iCa measurements <1·10–1·18 mmol/L.

Prevention

Prevention of citrate toxicity can be found in the controlled setting of an apheresis procedure. Studies have found that concurrent IV administration of calcium through the apheresis return line (typically 20 – 50 mg/kg/hour) is effective in reducing hypocalcemia, or citrate-related toxicity.

References [30-36]

COLD TOXICITY

Incidence	**Blood products**
• Unknown	• Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid) • Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled)

		Grade
Management	Active warming methods	1A
	Passive warming methods	1A
	Peritoneal lavage	1A
	Cardiopulmonary bypass	1A
Prevention	In-line blood warming devices	1A

Clinical findings & diagnosis

When RBC and plasma units, which are stored at refrigerated temperatures, are administered rapidly and in large volumes, hypothermia can result. Mild hypothermia (34-36ºC) can lead to shivering, and activation of sympathoneural and adrenomedullary responses, which in turn increase myocardial work and perfusion. In patients with flow-limiting coronary lesions, the increase in myocardial work can lead to myocardial ischemia and infarction. In severe hypothermia (<30ºC), cardiac conduction slows leading to cardiac fibrillation and cardiac arrest.

Other impacts of hypothermia include the slowing of temperature dependent enzymatic reactions, resulting in impaired citrate and lactate metabolism and delayed drug metabolism; and the impairment of the coagulation cascade and reduction of platelet function resulting in coagulopathy. Hypothermia can also increase the rate of wound infections in surgical patients by impairing neutrophil activity and decreasing subcutaneous blood flow. The vasoconstriction leads to decreases in subcutaneous oxygen tension which correlates with wound infection. Hypothermia also impairs the release of platelet-derived growth factors, which may contribute to poor wound healing.

Management

When a patient becomes hypothermic as a result of infusion of large volumes of cold blood products, a number of warming devices to increase the patient's core temperature can be used, starting with passive warming blankets to more sophisticated forced air warming devices. In extreme circumstances, warm peritoneal lavage and cardiopulmonary bypass can be used to warm patients.

Prevention

In-line blood warming devices intended for the infusion of blood products are available to rapidly warm blood products to a normal body temperature. These devices should be used when large volumes of blood products are being administered at high rates in order to help maintain the patient's core body temperature, thereby minimising adverse reactions associated with hypothermia.

References [37-42]

DELAYED HAEMOLYTIC TRANSFUSION REACTION (DHTR)

Incidence

- 1 of 2,500 hospitalized patients
- Up to 11% of sickle cell disease patients with previously detected antibodies
- Antibodies to low incidence antigens:1 per 650,000 RBC units

Blood products

- Red Blood Cells (RBCs) and Whole Blood

		Grade
Management	Red blood cell exchange transfusion	2C
	Anti-CD20 (rituximab) + methylprednisolone (SCD patients)	2C
Prevention	Extended RBC matching for chronic transfusion recipients	1A
	Antibody registry / medical records	1B
	For SCD and thalassemia patients: RBCs matched for Rh C, c, E, e, K blood group antigens	1A

Clinical findings & diagnosis

Delayed haemolytic transfusion reaction (DHTR) is the result of an amnestic immune system response in which a RBC antibody is detected 24 hours – 28 days post transfusion, accompanied with haemolysis. The clinical signs may include a fall in haemoglobin concentration or failure of increment post-transfusion, rise in indirect/total bilirubin, positive direct antiglobulin (Coombs') test (DAT) with elution of an alloantibody as well as other signs of clinical haemolysis, such as jaundice and renal impairment. Fatal cases are extremely rare. In SCD, diagnosis might be delayed when only anaemia and jaundice are present, as these symptoms might be attributed to veno-occlusive painful crisis with "hyperhaemolysis". In addition, reticulocytopenia might also appear in SCD after a DHTR (refer to Hyperhaemolytic Transfusion Reaction). Common antibodies responsible for DHTR belong to the following blood group systems: Rh; Kell; Duffy, Kidd, MNS, Diego.

Management

Communication between the blood bank and the clinical service is critical to ensure diagnostic understanding and accurate documentation. If correction of anaemia is needed, selection of RBC units that are negative for antigen the antibody is directed against is critical. Particular attention must be paid to serological compatibility for SCD due to precipitation of hyperhaemolysis. Exchange transfusions (manual or automatic) to prevent significant haemolysis might be helpful in cases where large amounts of RBCs have been recently transfused and the patient may not be able to tolerate haemolysis. Anti-CD20 (rituximab, 375 mg/m^2 twice, two weeks apart, or as fixed dose of 1000 mg) in combination with methylprednisolone (10 mg) have been proposed for patients with SCD, though there is evidence of resistance to treatment and concern about prolonged immunosuppression. Intravenous immunoglobulin (IVIG) may be attempted (0·5–1·0 mg/kg/day for 5 days) although data to support this practice is not available.

Prevention

A centralised recipient database that contains all historical RBC antibodies and the patient's extended RBC phenotype (serologic or genotype) can prevent reactions. The importance of the medical record review cannot be understated, as 25–60% of antibodies decrease to undetectable levels within 6 months. Extended RBC antigen matching also reduces the rate of RBC alloimmunisation in chronically transfused populations that have been studied (e.g., SCD patients). It is prudent to inform a patient of their RBC antibody status and counsel them on the need for antigen negative RBC transfusions, although there is no evidence to support that this will decrease the rate of DHTR/DSTR.

References [14, 43-65]

DELAYED SEROLOGIC TRANSFUSION REACTION (DSTR)

Incidence	**Blood products**
• 48·9–75·7 per 100,000 RBC units	• Red Blood Cells (RBCs) and Whole Blood

		Grade
Management	None	N/A
Prevention	Antibody registry / medical records	1B

Clinical findings & diagnosis

A delayed serologic transfusion reactions (DSTR) is defined as identification of a new clinically significant RBC antibody that is detected in a recipient 24 hours to 28 days after the transfusion. This previously undetected antibody may be found either in the serum or on the RBC surface (positive direct antiglobulin (Coombs') test (DAT)).

Patients who are at risk for DSTR/DHTR have had a previous immune response to foreign RBCs (through pregnancy or transfusion) and subsequently had this antibody decrease to levels undetectable by standard antibody screening. Twenty-five percent of RBC antibodies become undetectable using standard laboratory techniques over a median of 10 months (range 1 – 240) after initial development. Retrospective studies show that DSTR is more common than DHTR (0.66% versus 0.12%, respectively). The most common RBC antibodies implicated in DSTRs are anti-E (30%), anti-Jk^{a} (21%), anti-Fy^{a} (12%) and anti-c (12%).

Patients with DSTR do not experience clinical haemolysis whereas with delayed haemolytic transfusion reactions (DHTR) patients have clinical signs and symptoms of haemolysis. In the case of both DSTR and DHTR, the post-transfusion antibody development is an anamnestic immune response.

Management

By definition a DSTR occurs in the absence of clinical haemolysis. Still, the serological evidence (newly detected RBC alloantibody and/or a newly positive DAT) may warrant laboratory evaluation for haemolysis, such as haemoglobin concentration, indirect bilirubin, lactate dehydrogenase, and haptoglobin. When possible, a repeat antibody screen should be performed on the pre-transfusion sample to determine if there was error in detection, and recently transfused RBC units can be tested for their antigen status to pinpoint the cause. If the patient has evidence of haemolysis, the reaction should be managed as a DHTR (refer to Delayed Haemolytic Transfusion Reaction).

Prevention

The prevention of DSTRs consists of laboratory testing, prospective RBC antigen matching and meticulous review of medical records. In the blood bank laboratory, low-level RBC alloantibodies may be able to be detected if more sensitive test techniques are utilized. A central repository accessible across healthcare systems of patient RBC antibody histories can inform the transfusing facility of previously identified RBC antibodies, even if they are no longer detectable. Prospective RBC antigen matching has been shown to decrease the rate of alloimmunisation. It is prudent to inform patients of their RBC antibody status and counsel them on the need for antigen negative RBC transfusions, although there is no evidence to support that this will decrease the rate of DHTR/DSTR.

References [54-57, 66-68]

FEBRILE NON-HAEMOLYTIC TRANSFUSION REACTION (FNHTR)

Incidence

- RBCs: 1–3 per 100 units
- Platelets:
  - Whole blood-derived platelets (pools): 1·7 per 100 units
  - Apheresis: 1·4 per 100 units

Blood products

- Red Blood Cells (RBCs) and Whole Blood
- Platelets (Apheresis and Whole Blood Derived Pooled)
- Granulocytes

		Grade
Management	Antipyretics	1A
	Meperidine	1C
Prevention	Pre-storage leukocyte reduction	1A
	Plasma removal	2C
	Platelet additive solution	1B

Clinical findings & diagnosis

Fever is one of the most common symptoms reported with administration of blood products. In a febrile non-haemolytic transfusion reaction (FNHTR), a temperature elevation >1°C from baseline is usually accompanied by symptoms of cold, chills, rigours, and/or discomfort. The finding of elevated temperature plus additional findings may be due to the transfusion itself, or may be due to the patient's underlying illness or medical therapy. It is critical to consider more serious aetiologies, such as a septic transfusion reaction or an acute haemolytic transfusion reaction; when other causes have been excluded, a FNHTR may be diagnosed. Bacterial contamination should be suspected, particularly with reactions associated with platelet transfusions, as they are stored are room temperature.

The pathological mechanism for FNHTR is poorly understood, but is likely multifactorial including mechanisms that involved cytokines, patient antibodies, or other biological response modifiers that are elaborated from leukocytes in the blood product, or leukocyte antibodies in the donor unit interacting with patient leukocytes. Pre-storage leukocyte reduction has decreased the rate of FNHTR due to the decreased number of leukocytes remaining in the product during storage. With post-storage leukocyte reduction, the historical rate of 11-26% of transfusions yielded reactions. Plasma removal lowered the rate to 17%; and prestorage leukocyte reduction lowered it further to 1-2%.

Management

The transfusion must be stopped immediately with a rise in temperature and the patient managed supportively. It is critical to immediately perform a clerical check and laboratory testing to evaluate for more serious complications such as haemolysis from transfusion of an incorrect blood component. Standard dosing of antipyretics can be used to decrease the temperature and meperidine for shivering. If the patient is experiencing a cold reaction due to the temperature of the blood product, a blood warming device may be appropriate; refer to Cold Toxicity.

Prevention

As noted above the most effective preventative measure for FNHTR reactions is pre-storage leukocyte reduction of cellular blood products. Studies support that removal of plasma from the blood product by centrifugation and supernatant removal or by using platelet additives may further decrease the incidence of FNHTR. The use of antipyretics as a premedication has not been found to effectively prevent FNHTR.

References [27, 69-79]

HYPERHAEMOLYTIC TRANSFUSION REACTION (HHTR)		
Incidence • 1—19% in Sickle Cell Disease patients		**Blood products** • Red Blood Cells (RBCs) and Whole Blood
		Grade
Management	Prednisolone, oral	2C
	Intravenous immune globulin (IVIG)	2C
	Methylprednisolone	2C
	Anti-CD 20 (rituximab)	2C
	Plasma exchange	2C
Prevention	Intravenous immune globulin (IVIG)	2C
	Methylprednisolone	2C

Clinical findings & diagnosis

HHTR is a life-threatening haemolytic transfusion reaction, typically occurring in patients with haemoglobinopathies, but may be seen in other conditions. Diagnosis of HHTR is based on a decrease in haemoglobin concentration to levels below those before RBC transfusion and a fall in the absolute reticulocyte count. HHTR has been classified into acute and delayed forms. In general, the acute form occurs <7 days after RBC transfusion, the direct antiglobulin (Coombs') test (DAT) is usually negative and no RBC alloantibodies are identified. The delayed form usually occurs >7 days after RBC transfusion, the DAT is positive, and new RBC alloantibodies are often identified in patient's sample post-transfusion. Measurement of serum ferritin levels can be used to gauge haemolytic activity as well as the clinical response.

Management

For mild forms, oral prednisolone (1—2 mg/Kg/day) should be used initially. For severe forms, IVIG at a total dose of 2·0 g/Kg administered in 2 or 5 days in conjunction with IV methylprednisolone (4·0 mg/Kg for children and 0·5 g for adults for 2 days). Anti-CD20 (Rituximab) and plasma exchange were successful in very severe cases. Erythropoietin is not currently recommended.

Prevention

Awareness of HHTR is important because additional blood product transfusions may exacerbate haemolysis and may lead to a chronic protracted course or even death. If additional RBC transfusion is necessary, pre-medication with steroids and IVIG is recommended.

References [53, 80-88]

HYPOTENSIVE TRANSFUSION REACTION (HT)

Incidence	Blood products
• 0.004 – 1.32 per 100,000 units	• Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled)

		Grade
Management	No specific management; supportive care	N/A
Prevention	Begin new blood product	2C
	Washed cellular products	2C
	For a patient on an angiotensin-converting enzyme inhibitor (ACEi) Switch to another class of antihypertensive medication	2C

Clinical findings & diagnosis

Acute hypotensive transfusion reactions (HTs) are categorized by an abrupt drop in systolic and/or diastolic blood pressure by 30mm Hg or more that occurs within minutes of the start of the transfusion and resolves quickly once the transfusion is stopped. In these reactions, hypotension is the predominant manifestation; however other symptoms including respiratory, gastrointestinal or mild allergic symptoms may also be present. It is important to exclude other transfusion reactions where hypotension can be a manifestation such as acute haemolysis, septic, transfusion-related acute lung injury (TRALI), and anaphylaxis before making this diagnosis.

These reactions are believed to occur with activation of the intrinsic "contact activation" pathway of the coagulation cascade and generation of Bradykinnin (BK) and its active metabolite des-Arg^{9}-BK.[6] 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 a slow contraction of the intestinal smooth muscle, causing abdominal pain. Kinin metabolism is less efficient in the presence of an angiotensin-converting enzyme inhibitor (ACEi).

HTs are more likely to occur in patients that have had a previous hypotensive reaction, are on an ACEi, are being transfused with a negatively charged bedside leukocyte-reduction filter, undergoing apheresis or receiving platelets. These reactions have also been reported with bedside leukocyte-reduction using positively charged filters and pre-storage leukocyte filtration.

Other clinical scenarios where patients are at increased risk for hypotensive transfusion reactions include cardiopulmonary bypass, where the use of bypass pumps circumvent the BK-clearing by the pulmonary vasculature; individuals with an intrinsic anomaly of BK, des-Arg-BK or their degradation; and during radical prostatectomy where the release of human glandular kallikrein 2 during the surgical manipulation of prostatic tissue may facilitate BK and des-Arg-BK generation.

Management

As per all acute transfusion reactions, infusion of the blood component must be immediately stopped with prompt clinical assessment of the patient, and treatment with fluids and other supportive measures as indicated. No other management is needed for HTs; once transfusion is stopped the patient's blood pressure should normalize. Transfusion with the same unit should not be restarted as the symptoms are anticipated to recur.

Prevention

No routine preventative measures are indicated. If the patient is being treated with an ACEi and requires ongoing transfusion therapy, consider switching to another class of antihypertensive medication. If the transfusion episode was associated with a negatively charged bedside leukocyte reduction filter, then subsequent reactions can likely be prevented by avoiding the use of these filters.

References [89-104]

POST-TRANSFUSION PURPURA

Incidence	**Blood products**
• Unknown	• Red blood cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled)

		Grade
Management	Intravenous immune globulin (IVIG)	1B
	Plasma exchange	2C
Prevention	Leukocyte reduction, pre-storage	2A
	Avoidance of unnecessary transfusion	2A
	If transfusion required, HPA negative or washed cellular products	2C

Clinical findings & diagnosis

Post transfusion purpura (PTP) is defined as thrombocytopenia arising 5 to 12 days following transfusion of cellular blood components (RBCs or platelets). The onset of thrombocytopenia is usually rapid and the platelet count may fall from normal ranges to less than $10x10^9$/L within 24 hours. Associated clinical features may include widespread purpura, bleeding from mucous membranes, and in severe cases, intracranial haemorrhage and death.

The transfusion precipitating PTP causes a secondary immune response, increasing the levels of alloantibodies directed against specific human platelet antigen(s)(HPA). It usually affects HPA-1a negative individuals who have previously been alloimmunised by pregnancy (or, occasionally, transfusion). A complete understanding of the pathophysiology is unclear, including the mechanism of destruction of the patient's own antigen (HPA-1a) negative platelets, The Serious Hazards of Transfusion (SHOT) scheme has been collecting information on the number of cases of PTP with confirmed HPA alloantibodies since 1996: 52 out of the 53 cases were female, and alloantibodies with specificity for HPA-1a were the most common cause of PTP (either alone or in combination with other antibodies). The diagnosis of PTP can be confirmed by the detection of platelet specific alloantibodies (as mentioned, the majority are associated with the development of HPA-1a antibodies in HPA-1a negative patients).

Management

It is important to consider the diagnosis of PTP in a patient, typically a middle aged or elderly woman with a recent history of transfusion (RBC or platelet) and rapid onset of severe thrombocytopenia. Other causes of sudden thrombocytopenia (i.e. Heparin-induced thrombocytopenia) should be ruled out. Management is supportive. In untreated cases, the thrombocytopenia usually persists for between 7 and 28 days but may continue for longer. Immediate treatment may be required because of the risk of intracranial haemorrhage, which includes IVIG, steroids and plasma exchange. Platelet transfusions may be given, but may be associated with poor increments; there is no evidence that platelet concentrates from antigen (HPA-1a) negative platelets are more effective than those from random donors in the acute thrombocytopenic phase.

Prevention

Prevention of recurrence of PTP should include use of RBC and platelet units from HPA compatible donors (or autologous transfusion); some suggest washed cellular products to remove platelet membrane remnants. The patient should be provided with advice about the diagnosis. Leucocyte reduced blood components are required; based on the UK SHOT data, the annual number of reported cases has decreased since the introduction of universal leukocyte-reduction of cellular components in 1999.

References [48, 105-111]

SEPTIC TRANSFUSION REACTION (BACTERIAL CONTAMINATION)

Incidence

- Platelets:
  - Whole Blood (Pool of 5): 33.3 per 1,000,000 units
  - Apheresis: 9.1 – 14.3 per 1,000,000 units
- RBC: 0.56 per 1,000,000 units
- Plasma: 2.8 per 10,000,000 units

Blood products

- Platelets (Apheresis and Whole Blood Derived Pooled)
- Red Blood Cells (RBCs) and Whole Blood
- Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid)

		Grade
Management	Empiric broad-spectrum antibiotics	1A
Prevention	Diversion of first 10-50 mL of collection	1B
	Bacterial surveillance of platelet units	1B
	Pathogen reduction systems	1A

Clinical findings & diagnosis

Septic transfusion reactions frequently present during or within four hours of completion of transfusion. Fever, rigours, and hypotension are the most common signs/symptoms, but patients may also present with tachycardia, tachypnea, dyspnea, nausea, vomiting, shock, and disseminated intravascular coagulation. Definitive diagnosis of a septic transfusion reaction requires isolation of the same organism from the blood product and the patient. A septic reaction may be presumed in a culture-negative patient with clinical signs of sepsis if bacteria are isolated in the transfused unit. Other transfusion reactions with similar presentations (acute haemolytic, hypotensive, anaphylaxis) should be excluded. Gram negative infections typically present within 15 minutes of the start of transfusion.

Management

Infusion of the blood component must be immediately stopped with prompt clinical assessment of the patient, confirmation of patient identity, and notification of the blood bank. All recently transfused units should be evaluated for evidence of bacterial contamination including performance of gram stain and culture. Ideally, bacterial cultures (both aerobic and anaerobic) should be drawn from the patient prior to initiation of antibiotics. Broad-spectrum antibiotics such as β lactams and aminoglycosides should be started empirically. If the implicated unit is red blood cells, antibiotics with anti-*Pseudomonas* activity should be included.

Prevention

Blood collection centers have implemented procedures to reduce bacterial contamination: donor screening and proper disinfection of the skin prior to collection, diversion of the first 10-50 mL of blood collected, visual inspection prior to issue, and bacterial surveillance of platelet units. Because platelets are stored at room temperature, these units have the highest rate of bacterial contamination (1 in 3,000–5,000). However, many do not cause infection either because the units are removed from inventory based on positive bacterial surveillance results, or pre-transfusion storage time was insufficient to allow significant growth. Prompt reporting of suspected septic transfusion reactions to the blood bank enables quarantine of co-components from the same donor. Pathogen reduction (PR) systems, using UV light to cause crosslinking of nucleic acids with or without riboflavin or amotosalen, prevent growth of known and emerging viruses, bacteria, and parasites. These systems have been shown to be effective in decreasing the rate of septic transfusion reactions. There is evidence that PR affects platelet function and reduces post-transfusion corrected count increment, although this was not associated with increased bleeding incidence. There is some debate about the costs and benefits of implementing PR systems for platelet and plasma, which have been available in Europe since 2002 and were approved by the Food and Drug Administration (FDA) in the U.S in late 2014. PR systems for RBCS and whole blood are still in development.

References [3, 112-123]

TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD (TACO)

Incidence	Blood Products
• 1–8% of transfused recipients • 14·4 per 100,000 units	• Red Blood Cells (RBCs) and Whole Blood • Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid) • Platelets (Apheresis and Whole Blood Derived Pooled)

		Grade
Management	Diuretics or more aggressive fluid management strategies depending on the patient's renal function, supportive care	N/A
Prevention	Slow rate of infusion	2C
	Administer the minimum volume of blood products to achieve the clinical or laboratory parameter goal	2C
	Avoid concurrent administration crystalloids with blood products	2C
	Recognise patient risk factors for TACO and monitor vital signs closely for evidence of impending TACO	2C

Clinical findings & diagnosis

Transfusion-association circulatory overload (TACO) is under-recognised and under-reported entity; therefore, the incidence estimates are broad and it may be higher than reported. The initial presentation of TACO must be distinguished from TRALI, AHTR, and a septic transfusion reaction. There are no consensus criteria for the diagnosis of TACO, complicating reporting and incidence determination. Both the National Healthcare Safety Network (NHSN) Hemovigilance Module and Serious Hazards of Transfusion (SHOT) UK National Haemoviligance offer similar definitions of TACO, though with different timelines to presentation (6 or 4 hours, respectively). Patients present with new onset or acute exacerbation of 3 or more of the following during or within 4-6 hours of transfusion: respiratory distress (dyspnea, orthopnea, cough); elevated brain natriuretic peptide (BNP, or NT-pro-BNP); elevated CVP; evidence of left heart failure; evidence of positive fluid balance; and radiographic evidence of pulmonary edema (not always present, especially if TACO is interdicted early in its course). The presence of elevated BNP, or NT-pro-BNP is controversial due to the short storage half-life of BNP at 4ºC, some literature indicates that an increase in the post-reaction BNP by ≥1·5 times the pre-transfusion level is suggestive of TACO. In the absence of a pre-transfusion BNP level, an elevated post-reaction level can identify a patient at risk for TACO.

Patient risk factors include older age (although TACO can also occur in young recipients), renal failure (especially dialysis dependent), preexisting fluid overload, cardiac dysfunction (including CHF, ventricular hypertrophy, valvular disease), administration of large volumes of blood products (although TACO can occur following the administration of small quantities of blood products), rapid administration rate, recent surgery, mechanical ventilation and recent administration of vasopressors.

Management

Stop the transfusion; often this is sufficient for the symptoms to abate, especially if the patient has reasonable cardiac and renal function. Supplemental oxygen can be administered as necessary. Diuretic administration can be diagnostic and therapeutic for a TACO although care must be taken in patients with haemodynamic instability so as to not exacerbate or precipitate hypotension

Prevention

Careful assessment of patient's pre-transfusion fluid balance and risk factors for TACO can indicate those at risk for TACO and the following measures taken to reduce the likelihood of a reaction occurring: administer transfusions slowly over 3-4 hours, check vitals often, administer diuretics if the patient is haemodynamically stable and fluid overloaded, only administer the minimum required quantity of blood products to achieve the clinical or laboratory parameter endpoint (i.e., 1 unit at a time); avoid co-administration of crystalloids. Blood bank can split blood products into aliquots; each aliquot can be administered slowly over 3-4 hours thereby increasing the time over which transfusion is administered.

References [13, 23, 124-127]

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD)

Incidence	**Blood products**
• Irradiation products: Risk near 0% • Pathogen inactivated products: Risk near 0%	• Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled) and HLA-matched platelets • Granulocytes

		Grade
Management	Hematopoietic stem cell transplant	N/A
Prevention	Treatment of cellular components with gamma or X-Irradiation or pathogen inactivation/reduction with ultraviolet irradiation	1B

Clinical findings & diagnosis:

Transfusion associated graft versus host disease (TA-GVHD) occurs when transfused donor lymphocytes escape destruction by host immune cells, recognise their new host as foreign and mount an attack. Severely immunosuppressed patients lacking functional T cells are at greatest risk (i.e. patients who are immunosuppressed due to chemotherapeutic agents, and patients with congenital T cell deficiencies such as DiGeorge or Severe Combined Immunodeficiency Syndrome). Immuno-competent patients are also at risk when receiving cellular components from a donor with whom the recipient shares an HLA haplotype and where the donor is HLA homozygous for the haplotype for which the recipient is heterozygous; this scenario can occur when transfusing HLA matched platelets, blood components collection from first- or second-degree relatives, or in communities/countries where there is limited HLA diversity. This disparity makes the mismatched allele appear foreign to only the donor lymphocyte, leading to an uncontested immune response.

The signs and symptoms of TA-GVHD develop within 5 – 10 days after transfusion. Patients present with an erythematous maculopapular rash, fever, abdominal pain, diarrhea, nausea and vomiting. TA-GVHD is distinguishable from transplant associated GVHD in that the attacking lymphocytes target bone marrow hematopoietic progenitor cells, and as a result, the patient develops irreversible and complete bone marrow aplasia. Laboratory tests show pancytopenia, abnormal liver function and electrolyte disturbances. A skin biopsy from the affected area may help make the diagnosis. Full marrow aplasia, evident on bone marrow biopsy, usually develops within 21 days of transfusion.

Management:

Supportive as TA-GVHD is nearly always fatal with death usually attributable to pancytopenia / infections.

Prevention:

TA-GVHD is prevented by using gamma or X-irradiation, or pathogen inactivation/reduction with ultraviolet radiation**.** Leukoreduction is not sufficient for prevention; however recent data from SHOT suggests that there may be a threshold effect for the number for T cells needed to cause TA-GVHD.

Indications for irradiation	**Possible indications**	**Irradiation not indicated**
• Hematopoietic stem cell transplant patients • Congenital immunodeficiency affecting T cells • Hodgkin's disease, continued for life • Intrauterine transfusions (IUT) preterm low birth weight neonates • Neonatal exchange transfusions • High-dose chemotherapy or radiotherapy • Purine-analogue drugs (e.g. fludarabine, cladribine, pentostatin, bendamustine, clofarabine) • Alemtuzumab (CamPath) • Antithymoglobulin (ATG) • Granulocyte transfusions • Cellular components from 1st/ 2nd degree relatives	• Solid organ transplant patients • Infants up to 6 months • Healthy premature infants until 6-12 months of age	• HIV/AIDS patients • Acute or chronic leukemia • Aplastic anaemia • Lymphoma other than Hodgkin's • Severe leukopenia • Autoimmune diseases • High-dose steroids • Azathioprine • Cyclosporine • Mycophenolate mofetil • Rituximab

• HLA-matched, HLA-selected or cross-matched platelet units		
References [13, 128-137]		

TRANSFUSION-ASSOCIATED HYPERKALEMIC CARDIAC ARREST (TAHCA)

Incidence	**Blood products**
• Unknown	• Red Blood Cells (RBCs) and Whole Blood, particularly irradiated units and units with a longer storage age

		Grade
Management	Insulin, glucose, calcium gluconate and furosemide	1A
Prevention	Identify patients at risk for developing TAHCA	2C
	Transfuse "fresh" blood (≤7—10 days)	2C
	Transfuse irradiated RBC units as soon as possible after irradiation	2C
	Wash or plasma reduce older or previously irradiated RBC units	1B
	Transfuse RBCs with in-line potassium filter	1B

Clinical findings & diagnosis

Stored RBC units may contain a sufficient amount of supernatant potassium to result in hyperkalemia if large volumes are transfused, mainly to paediatric recipients. Available evidence suggests that TAHCA usually happens with large or rapidly transfused volumes, particularly in patients with an associated hypovolemia. The following risk factors have been identified as contributors for TAHCA: longer storage age of the RBC product, irradiation of RBCs, rate and volume of RBC products transfused, young patient age and small total blood volume of patient, and presence of comorbidities (hyperglycemia, hypocalcemia, hypothermia, acidosis, and renal insufficiency).

Management

Several strategies have been reported to manage post-transfusion hyperkalemia, such as administration of 10% calcium gluconate – 1 mg/kg IV over 5—10 minutes, 0·25—0·50 grams glucose per kg plus 0·3 units insulin per gram glucose IV over 30—60 minutes, consideration of furosemide 1 – 2 mg/kg.

Prevention

Because the majority of TAHCA cases have been reported in the perioperative setting, it is important to identify at-risk patients (i.e. patients with low total blood volume who will receive a large volume of RBCs in a short period of time). In this scenario, particularly for children, the maximum infusion rate should be 0.5 mL/Kg/min. In these recognised circumstances, it is advisable to periodically monitor potassium levels so that potassium lowering strategies can be implemented thereby preventing cardiac arrest. Use of filters or ultrafiltration can decrease potassium content before transfusion administration. Selection of "fresh" blood (generally considered ≤7–10 days) and washed or plasma reduced / centrifuged RBC units are also effective in preventing this reaction.

References [3, 138-146]

TRANSFUSION ASSOCIATED NECROTISING ENTEROCOLITIS (NEC)

Incidence	**Blood products**
• Unknown	• Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled)

		Grade
Management	Supportive care, including surgery	1B
Prevention	Withhold feeding during transfusion	2C
	Leukocyte reduction, pre-storage	2C
	Avoidance of unnecessary transfusion	2C

Clinical findings & diagnosis

Necrotising enterocolitis (NEC), a common disease in preterm and very low birth weight neonates, is associated with significant morbidity and mortality. The clinical features include abdominal distention and blood in stool. NEC may be diagnosed definitely at surgery or at post-mortem examinations. Preterm neonates are a heavily transfused group (57%). This has raised suggestions of an association between transfusion and NEC. Although the pathogenesis of NEC is unknown, immunological dysregulation and host immaturity may be relevant factors. Therefore, it has been hypothesized that an entity termed transfusion associated necrotising enterocolitis may exist which shares mechanisms with reactions such as transfusion related acute lung injury (TRALI) [hence the related term 'transfusion related acute gut injury' (TRAGI)]. The role of transfusions and the development or severity of clinical course of NEC remains controversial.

It should be noted that infants who participated in the recent large 'Age of Red Blood Cells in Premature Infants' (ARIPI) trial were exposed to a significant volume and frequency of RBC transfusions at different storage ages, but there were no differences in rates of severe NEC between study arms. Associations between use of platelet transfusions and NEC have also been suggested, but the literature is very sparse.

In summary, there is no accepted mechanism for transfusion associated-NEC or agreement that the syndrome exists. Some studies report that recent exposure in the previous 48 hours to RBC transfusion may be associated with NEC, or that transfusion associated-NEC may be more severe with more cases requiring surgery. Literature describing any association is dominated by retrospective case control studies with moderate risk of bias. Prospective studies are required to assess the causality of any association between transfusion associated-NEC and transfusion.

Management

The management of NEC is supportive including surgery.

Prevention

Preventative strategies to NEC are general and specific. Local guidelines to reduce inappropriate use of RBC transfusions consistent with evidence should be promoted and audited. A few studies have addressed the issue of withholding feeds around the time of transfusion; these studies are non-interventional, and preclude firm practice recommendations.

References [147-155]

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

Incidence

Current risk estimates per component transfused after full implementation of immune mediated risk mitigation strategies:

- Plasma: 0.4 per 100,000 units
- Apheresis Platelets: 1 per 100,000 units
- Red Blood Cells: 0.5 per 100,000 units
- Whole Blood, granulocytes: unknown
- Cryoprecipitate: unknown
- Plasma derivatives: extremely rare

Blood products

- Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid)
- Platelets (Apheresis and Whole Blood Derived Pooled)
- Red Blood Cells
- Whole Blood
- Granulocytes
- Cryoprecipitate
- Plasma derivatives (IVIG, RhIG)

		Grade
Management	Supportive Care	1A
	Extracorporeal membrane oxygenation	2C
Prevention	Platelet additive solutions	2C
	Washed cellular products	2C
	Screening & selecting blood donors	2C

Clinical findings & diagnosis

Diagnosis is based on clinical and radiographic findings and temporal association with transfusion. TRALI may be difficult to distinguish from other causes of acute lung injury. The clinical presentation includes dyspnea, tachypnea and hypoxemia, sometimes accompanied by rigours, tachycardia, fever, hypothermia and hypotension or hypertension. In mechanically ventilated patients, copious frothy pink-tinged fluid may be recovered from the endotracheal tube, but this finding is non-specific. Bilateral interstitial infiltrates are present on chest radiograph but are also non-specific and difficult to distinguish from overload edema. Transient leukopenia may be observed. Other types of acute transfusion reactions with similar presentations (transfusion-associated circulatory overload (TACO), septic and anaphylactic transfusions reactions) should be excluded.

Management

As per all acute transfusion reactions, infusion of the blood component must be immediately stopped with prompt clinical assessment of the patient, confirmation of patient identity, examination of the transfused component and notification of the blood bank. Management of TRALI is supportive with supplemental oxygen or mechanical ventilation, as needed, and application of restrictive tidal volume ventilation and a restrictive fluid strategy as per other causes of acute lung injury. There is no role for steroids The use of extracorporeal membrane oxygenation (ECMO) has been reported for two severe cases.

Prevention

Risk associated with high volume plasma containing products has decreased significantly as a result of risk mitigation efforts. Prevention measures include application of a restrictive transfusion strategy to avoid unnecessary transfusions, recognition of populations at increased risk for acute lung injury and reduction of modifiable risk factors. Awareness and reporting of suspected TRALI to the blood bank enables quarantine of other components from the same donor and investigation, testing and exclusion of antibody positive donors from the donor pool. Use of platelet concentrates re-suspended in platelet additive solution (PAS) or washed cellular components (red blood cells, platelets, granulocytes) to reduce amount of transfused plasma and/or decrease antibody titres or biological response modifiers associated with TRALI has been proposed but these approaches are not commonly used at this time due to uncertain benefit. Prothrombin complex concentrates may be used instead of plasma when available and medically indicated.

References [3, 156-164]

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