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Supplementary appendix

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**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

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ACUTE HAEMOLYTIC TRANSFUSION REACTION (AHTR), NON-IMMUNE		
Incidence	Blood products	Grade
<ul style="list-style-type: none"> Rare, but likely under reported 	<ul style="list-style-type: none"> Red Blood Cells (RBCs) and Whole Blood 	
Management	No specific management; supportive care	N/A
Prevention	Adherence to all guidelines on appropriate RBC transport, handling and infusion	1A
Clinical findings & diagnosis		
<p>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 through 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.</p> <p>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).</p> <p>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.</p> <p>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.</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
References ^{12, 14-17}		

ANAPHYLACTIC TRANSFUSION REACTION		
Incidence	<ul style="list-style-type: none"> 8 per 100,000 units 	Blood products <ul style="list-style-type: none"> Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid) Red Blood Cells (RBCs) and Whole Blood Platelets (Apheresis and Whole Blood Derived Pooled) Granulocytes
Management	Epinephrine/Adrenaline High-flow supplemental oxygen, rapid fluid administration with crystalloid solution (0.9% saline) Second line medications: Antihistamine (H ₁ and H ₂ antihistamines), Bronchodilator therapy, Glucocorticoids	Grade
		1A
		1C
		1C
Prevention	Discuss with allergist/immunologist and transfusion physician Administer transfusion in a clinical area with direct observation & resuscitation capabilities Transfuse with plasma-reduced (washed) cellular components Premedication with antihistamine	1C 2C 2C 2C
Clinical findings & diagnosis		
<p>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:</p> <ul style="list-style-type: none"> 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 <p>Mechanisms include activation of mast cells and basophil granulocytes with mediator release.</p>		
Management		
<p>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: H₁- 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 [(β₂-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 H₂-antihistamine [e.g. Ranitidine 50 mg (adult) or 1 mg/kg, maximum 50 mg (child)].</p>		
Prevention		
<p>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.</p>		
References 3, 18-20, 22, 26-29		

CITRATE TOXICITY		
Incidence		Blood products
<ul style="list-style-type: none"> Unknown 		<ul style="list-style-type: none"> Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid) Red Blood Cells (RBCs) and Whole Blood Platelets (Apheresis and Whole Blood Derived Pooled)
Management	Calcium administration	Grade
Prevention	Calcium administration	1A 1B
Clinical findings & diagnosis		
<p>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.</p> <p>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.</p> <p>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.</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
References ³⁰⁻³⁶		

DELAYED HAEMOLYTIC TRANSFUSION REACTION (DHTR)	
Incidence <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Red Blood Cells (RBCs) and Whole Blood
Management Red blood cell exchange transfusion Anti-CD20 (rituximab) + methylprednisolone (SCD patients)	Grade 2C 2C
Prevention Extended RBC matching for chronic transfusion recipients Antibody registry / medical records For SCD and thalassemia patients: RBCs matched for Rh C, c, E, e, K blood group antigens	1A 1B 1A
Clinical findings & diagnosis <p>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.</p>	
Management <p>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/m² 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.</p>	
Prevention <p>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.</p>	
References ^{14, 43-65}	

DELAYED SEROLOGIC TRANSFUSION REACTION (DSTR)		
Incidence	<ul style="list-style-type: none"> 48.9–75.7 per 100,000 RBC units 	Blood products <ul style="list-style-type: none"> Red Blood Cells (RBCs) and Whole Blood
Management	None	Grade N/A
Prevention	Antibody registry / medical records	1B
Clinical findings & diagnosis <p>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)).</p> <p>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%).</p> <p>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.</p>		
Management <p>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).</p>		
Prevention <p>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.</p>		
References 54-57, 66-68		

FEBRILE NON-HAEMOLYTIC TRANSFUSION REACTION (FNHTR)		
Incidence	<ul style="list-style-type: none"> • RBCs: 1–3 per 100 units • Platelets: <ul style="list-style-type: none"> • Whole blood-derived platelets (pools): 1.7 per 100 units • Apheresis: 1.4 per 100 units 	Blood products <ul style="list-style-type: none"> • Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled) • Granulocytes
Management	Antipyretics Meperidine	Grade 1A 1C
Prevention	Pre-storage leukocyte reduction Plasma removal Platelet additive solution	1A 2C 1B
Clinical findings & diagnosis		
<p>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 at room temperature.</p> <p>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%.</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
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
Management	Prednisolone, oral Intravenous immune globulin (IVIG) Methylprednisolone Anti-CD 20 (rituximab) Plasma exchange	Grade 2C 2C 2C 2C 2C
Prevention	Intravenous immune globulin (IVIG) Methylprednisolone	2C 2C
Clinical findings & diagnosis		
<p>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.</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
References <small>53, 80-88</small>		

HYPOTENSIVE TRANSFUSION REACTION (HT)		
Incidence	<ul style="list-style-type: none"> • 0.004 –1.32 per 100,000 units 	Blood products <ul style="list-style-type: none"> • Red Blood Cells (RBCs) and Whole Blood • Platelets (Apheresis and Whole Blood Derived Pooled)
Management	No specific management; supportive care	Grade N/A
Prevention	Begin new blood product Washed cellular products For a patient on an angiotensin-converting enzyme inhibitor (ACEi) Switch to another class of antihypertensive medication	2C 2C 2C
Clinical findings & diagnosis		
<p>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.</p> <p>These reactions are believed to occur with activation of the intrinsic “contact activation” pathway of the coagulation cascade and generation of Bradykinin (BK) and its active metabolite des-Arg⁹-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).</p> <p>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.</p> <p>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.</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
References ⁸⁹⁻¹⁰⁴		

POST-TRANSFUSION PURPURA		
Incidence		Blood products
<ul style="list-style-type: none"> Unknown 		<ul style="list-style-type: none"> Red blood cells (RBCs) and Whole Blood Platelets (Apheresis and Whole Blood Derived Pooled)
Management	Intravenous immune globulin (IVIG)	Grade
	Plasma exchange	1B
Prevention	Leukocyte reduction, pre-storage	2C
	Avoidance of unnecessary transfusion	2A
	If transfusion required, HPA negative or washed cellular products	2A
		2C
Clinical findings & diagnosis		
<p>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 $10 \times 10^9/L$ within 24 hours. Associated clinical features may include widespread purpura, bleeding from mucous membranes, and in severe cases, intracranial haemorrhage and death.</p> <p>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).</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
References <small>48, 105-111</small>		

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, rigors, 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	<ul style="list-style-type: none"> • 1–8% of transfused recipients • 14.4 per 100,000 units 	Blood Products <ul style="list-style-type: none"> • Red Blood Cells (RBCs) and Whole Blood • Plasma (FFP, FP24, Thawed, Cryoprecipitate Reduced, Liquid) • Platelets (Apheresis and Whole Blood Derived Pooled)
Management	Diuretics or more aggressive fluid management strategies depending on the patient's renal function, supportive care	Grade 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		
<p>Transfusion-associated 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 Haemovigilance 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 4°C, 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.</p> <p>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.</p>		
Management		
<p>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</p>		
Prevention		
<p>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.</p>		
References		
13, 23, 124-127		

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD)		
Incidence <ul style="list-style-type: none"> Irradiation products: Risk near 0% Pathogen inactivated products: Risk near 0% 	Blood products <ul style="list-style-type: none"> Red Blood Cells (RBCs) and Whole Blood Platelets (Apheresis and Whole Blood Derived Pooled) and HLA-matched platelets Granulocytes 	
Management Prevention	Hematopoietic stem cell transplant Treatment of cellular components with gamma or X-Irradiation or pathogen inactivation/reduction with ultraviolet irradiation	Grade N/A 1B
Clinical findings & diagnosis: <p>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.</p> <p>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.</p>		
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 <ul style="list-style-type: none"> 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 	Possible indications <ul style="list-style-type: none"> Solid organ transplant patients Infants up to 6 months Healthy premature infants until 6-12 months of age 	Irradiation not indicated <ul style="list-style-type: none"> 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

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| • HLA-matched, HLA-selected or cross-matched platelet units | | |
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References ^{13, 128-137}

TRANSFUSION-ASSOCIATED HYPERKALEMIC CARDIAC ARREST (TAHCA)		
Incidence	Blood products	
<ul style="list-style-type: none"> Unknown 	<ul style="list-style-type: none"> Red Blood Cells (RBCs) and Whole Blood, particularly irradiated units and units with a longer storage age 	
Management	Insulin, glucose, calcium gluconate and furosemide	Grade 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		
<p>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).</p>		
Management		
<p>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.</p>		
Prevention		
<p>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.</p>		
References 3, 138-146		

TRANSFUSION ASSOCIATED NECROTISING ENTEROCOLITIS (NEC)	
Incidence <ul style="list-style-type: none"> Unknown 	Blood products <ul style="list-style-type: none"> Red Blood Cells (RBCs) and Whole Blood Platelets (Apheresis and Whole Blood Derived Pooled)
Management Supportive care, including surgery Prevention Withhold feeding during transfusion Leukocyte reduction, pre-storage Avoidance of unnecessary transfusion	Grade 1B 2C 2C 2C
Clinical findings & diagnosis <p>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.</p> <p>It should be noted that infants who participated in the recent large ‘Age of Red Blood Cells in Premature Infants’ (ARIP) 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.</p> <p>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.</p>	
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)		
<p>Incidence Current risk estimates per component transfused after full implementation of immune mediated risk mitigation strategies:</p> <ul style="list-style-type: none"> • 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 	<p>Blood products</p> <ul style="list-style-type: none"> • 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) 	
<p>Management</p>	<p>Supportive Care Extracorporeal membrane oxygenation</p>	<p>Grade 1A 2C</p>
<p>Prevention</p>	<p>Platelet additive solutions Washed cellular products Screening & selecting blood donors</p>	<p>2C 2C 2C</p>
<p>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.</p>		
<p>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.</p>		
<p>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.</p>		
<p>References ^{3, 156-164}</p>		

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