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Complications of Allogeneic Blood Transfusion : Current Approach to Diagnosis and Management

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ABSTRACT

Introduction : Blood transfusion remains a vital component of modern medicine, as yet artificial blood or blood substitute is still widely promising. In well-organized health care systems, with standard transfusion services/facilities and safe practices, the risk associated with infusion of allogeneic blood components is minimal or negligible. However, in most developing nations,

significant morbidity is still associated with allogeneic blood transfusion.

Objective : This article is a review on diagnosis of transfusion reactions and modalities for treatment, aimed at promoting interest and awareness as well as, providing current knowledge regarding blood transfusion complications among clinical staff involved in transfusion care.

Methodology : Relevant literatures were searched

using search engines such as PubMed and Google Scholar, as well as standard textbooks in transfusion medicine. Results were summarized in appropriate sections.

Results : There are several complications associated with allogeneic blood transfusion. Many of these complications can be prevented and controlled through effective donor and recipient haemovigilance, as well as training and re-training of both clinical and blood bank staff.

Conclusion : Improved knowledge regarding these complications, as well as current treatment guidelines is a crucial strategy to their prevention and control in developing nations. This will invariably increase the capacity and ability of the attending clinical staff (physicians/nurses) to correctly identify, manage and report these adverse transfusion reactions.

Keywords : Blood transfusion; transfusion reactions; complications; allogeneic blood; developing countries; diagnosis and management; prevention of transfusion reactions.

1. INTRODUCTION

Blood transfusion refers to therapeutic infusion of blood, blood components and blood products into an individual in order to meet a specific physiologic need. As yet, laboratory synthesis or culture of blood components is still neither practically possible nor commercially available, safe transfer of blood from the donor to the recipient must be ensured [1–3]. While researches are directed at commercial production of artificial blood, current practices must aim at zero tolerance for blood transfusion reactions [1-3]. There is therefore a need for effective haemovigilance system particularly in developing nations.

There are several notable complications of allogeneic blood transfusion. Since the inception of transfusion practices, transfusion safety has been a major concern and challenge. Earliest attempts at blood transfusion were fraught with life-threatening complications such as acute haemolytic transfusion reactions [4,5]. However, the discovery of ABO blood group system by Karl Landsteiner in 1901 provided the much needed clinical insights into the

immunologic basis of transfusion reactions [6,7]. This paved the way for today's routine immune pre-compatibility testing of blood units. However, transfusion reactions were not limited to immunologic causes alone. In the 1970s prior to routine viral screening of blood components and prior to discovery of HIV in 1983, a significant proportion of haemophiliacs and other patients regularly transfused with blood components developed acquired immunodeficiency syndrome (AIDS) [8-10]. These observations propelled the quest for invention of reliable methods of detecting and curbing transfusion transmissible infections (TTIs) [11]. Up until this moment, myriad of complications have been reported and described in association with blood transfusion. Incidence of many of these complications has been controlled to the barest minimum in most developed nations [12-15]. Conversely, haemovigilance systems in developing African/Asian nations including Nigeria are poor or even non-existent [16]. On a global scale, the incidence of transfusion reactions range from less than 1% in US to as

high as 8.7% in developing countries [17-19].

In view of the burden and potential hazards associated with blood transfusion especially in developing nations, it is pertinent to review the current definitions and differential diagnosis of blood transfusion-related complications, their treatment and prevention. Improved knowledge among hospital clinical staff (transfusionist) will foster better awareness and improved transfusion care, especially in developing nations. As well, it provides a practical framework for developing local/institutional protocols that are geared towards implementing a more effective haemovigilance system.

Relevant local and foreign literatures on epidemiology, diagnosis and management of transfusion reactions were sought, collated and summarized in appropriate sections of this manuscript. Searches were performed using search engines such as google scholar, PubMed, as well as standard textbooks in transfusion medicine. Search words such as complications, allogeneic blood, transfusion medicine and epidemiology were used.

2. CURRENT TRENDS IN TRANSFUSION MEDICINE

The current scope of transfusion medicine goes beyond the traditional infusion of blood to include infusions of peripheral stem cells, recombinant coagulation proteins and use of haemopoiesis stimulating drugs such as erythropoietin and aphaeresis technology [20,21]. In today's practice, infusion of whole blood is hardly indicated except cases of significant acute blood loss, autologous blood transfusions, as well as neonatal/intrauterine transfusions. Blood components are therapeutic components of blood intended for transfusion. Blood product refers to therapeutic products, derived from blood or plasma, produced through a manufacturing process [21].

In today's transfusion practice, whole blood therapy is hardly utilized. However, this may not be the case in most developing nations, including Nigeria. Ideally, specialist blood components such as red cell concentrates, platelets, fresh frozen plasma (FFP) and cryoprecipitate are administered to individual patients as indicated. Even

where multiple transfusion needs are present as in a patient with symptomatic severe pancytopenia, each specific component is administered. The practice of blood component therapy (BCT) is associated with improved utility of blood (a single whole blood unit may be separated into three different components for possible use by three different patients) [22]. Further to this, BCT reduce unnecessary patient exposure to non-therapeutic fractions of the whole blood being transfused, resulting in fewer complications. In the long run, BCT if well practiced reduces blood supply needs and the overall cost of transfusion practice [23].

Blood components are prepared through centrifugation technique or aphaeresis [24]. Aphaeresis refers to extraction of specific cells from a blood donor using a programmed machine. Aphaeresis components are more effective and preferable to red cells/platelets prepared by cold centrifugation. The major therapeutic benefits of aphaeresis include automation, reduced recipient exposure to multiple donors, thus

reducing the risk of immunologic transfusion reactions and TTIs [24,25].

3. COMPLICATIONS OF BLOOD TRANSFUSION

These are undesirable and unintended response or effects during or after administration of blood, blood components or blood products, that can be associated with a said product. Simply put, they are adverse transfusion reactions or hazards of blood transfusion [20]. Transfusion reactions are categorized based on the timing of onset or its underlying

pathophysiologic mechanisms, as shown in Table 1. A transfusion reaction is said to be acute if it occurs during or within 24 hours of transfusion or delayed if it occurs beyond 24 hours up to 4 weeks after transfusion.

Acute transfusion reactions (ATR) occur at a rate of 0.5–3% [26]. Long-term complications such as iron overload, TTIs occurs and persists for months or years after transfusion episodes. Transfusion reactions may also be immune mediated or non-immunologic [20].

Table 1. Complications of blood transfusion

ACUTE COMPLICATIONS	DELAYED/LONG-TERM COMPLICATIONS
IMMUNOLOGIC <ul style="list-style-type: none"> • Allergic reactions • Febrile non-haemolytic transfusion reactions • Anaphylactic reaction • Transfusion related acute lung injury • Acute haemolytic transfusion reaction 	IMMUNOLOGIC <ul style="list-style-type: none"> • Delayed haemolytic transfusion reaction • Delayed serologic transfusion reaction • Allo-immunization • Transfusion associated Graft Versus Host Disease • Post transfusion purpura
NON-IMMUNOLOGIC <ul style="list-style-type: none"> • Bacterial contamination/sepsis • Transfusion associated circulatory overload • Clotting abnormalities • Metabolic complications: citrate toxicity, hyperkalaemia, hypocalcaemia, hypothermia, etc Others: Air embolism 	NON IMMUNOLOGIC <ul style="list-style-type: none"> • Transfusion transmissible infections • Thrombophlebitis • Iron overload

4. ACUTE COMPLICATIONS AND TREATMENT GUIDELINES

4.1 Febrile Non-haemolytic Transfusion Reactions

Febrile non-haemolytic transfusion reaction (FNHTR) is the commonest immediate complication of

blood transfusion [19,20,27,28]. It is almost always associated with infusion of cellular components and rarely plasma components. Its incidence is higher with transfusion of whole blood derived platelet concentrates (4.6%)

compared to red cell transfusions (0.33%) [29]. FNHTR is more frequent in multi-transfused persons as well as multi-parous women. Immune and non-immune mechanisms are implicated in its aetiology. FNHTR is considered a form of systemic inflammatory response syndrome (SIRS) which results from exposure to antigenic stimuli in the donor blood. In most settings, the recipient has been sensitized to the implicating antigen usually HLA antigens on leucocytes or less frequently human platelet antigens and neutrophil specific antigens, that are lacking in the recipient [20]. The resultant antigen-antibody interaction triggers systemic inflammation with release of pyrogenic cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). With increasing length of storage, the levels of cytokines in stored components also increase, explaining why FNHTR is more frequent in stored blood components [29]. Clinically, patients with FNHTR develop fever (at least 38°C) or at least 1°C rise above baseline, within 30 to 90 minutes of commencement of transfusion. Fever may be associated with chills, rigors

and headaches [20]. Diagnosis of FNHTR requires exclusion of other causes of fever including pre-transfusion morbidities, life threatening transfusion reactions such as septic transfusion reactions, transfusion related acute lung injury (TRALI) and acute haemolytic transfusion reaction (AHTR). Often times, FNHTR are more troublesome than dangerous especially in situations mediated by very potent lymphocytotoxic HLA antibodies. Treatment guidelines for FNHTR are suggested in Table 2 below [29-31].

Although, there are strong arguments for and against universal leucoreduction of blood products [35], the potential benefits in support of universal leucodepletion as practiced in some nations is related to preventing transmission of prions and cytomegalovirus, prevention of transfusion related immune-modulation (TRIM), besides reducing the incidence of FNHTR. However, cost-benefit analysis suggests that leucodepletion does not have a favorable cost effectiveness ratio in relation to the incidence of FNHTR [36].

Table 2. Treatment of febrile non-haemolytic transfusion reactions

1. The goal of treatment is to relieve symptoms and prevent recurrences.
2. Patients with prior history of FNHTR should be pre-medicated with antipyretics before onset of transfusions
3. At the outset of FNHTR, blood transfusion should be temporarily discontinued until life threatening differentials of transfusion pyrexia such as AHTR is excluded.
4. Intravenous access should be maintained with isotonic saline.
5. Antipyretics should be administered immediately in order to relieve the fever. Oral acetaminophen should be given at a dose of 500–1000mg in adults or 10–15 mg/kg in children. NSAIDS should be avoided.
6. If rigor is persistent, it may be controlled with morphine 2–4 mg intravenously (IV) stat. Meperidine (pethidine) 25–50 mg IV should be avoided due to its potentials for neurotoxicity.
7. If there is inter-current allergies/urticaria, antihistamines such as diphenhydramine, chlorpheniramine or promethazine should be administered.
8. In patients that are refractory to the above regimen, gluco-corticoids are indicated. Hydrocortisone IV should be administered at a dose of 100 mg stat (adults) or 1–2 mg/kg in children.
9. If symptoms are controlled within 30 minutes to an hour, transfusion should be resumed at a slower rate.
10. In patients with prior history of FNHTR, pre-medication with hydrocortisone 100 mg IV 4–6 hours before commencement of transfusion and or other antipyretics prevents FNHTR.
11. Transfusion should be administered at a slow rate after symptoms abate.
12. Pre-storage leucodepletion of blood component reduces the risk of FNHTR [32-34].

Due to its lack of cost-effectiveness, universal leuco-depletion of blood components may not be practical in most developing nations. However, leucodepletion should be favourably considered in selected cases including neonatal transfusions, history of prior FNHTR and haemopoietic stem cell transplant (HSCT) recipients.

4.2 Acute Haemolytic Transfusion Reaction

Acute haemolytic transfusion reaction (AHTR) is the most dangerous early complication of blood transfusion. It is frequently associated with human errors such as mislabeling of samples, patient misidentification, erroneous interpretation of tests, misrecording/transcription errors and other clerical issues. Incidence is about 1 per 600,000 red cell transfusions, with mortality rate of about 5 to 10%. Overall, the incidence of haemolytic transfusion reaction is in the range of 1 per 10000 to 50000 blood components transfused [37–39]. Often times, AHTR is associated with ABO antigens and majority of AHTR are caused by

mismatch blood transfusions [12]. Non-ABO antigens such as Rh and Kell antigens are also implicated, especially in the extravascular forms. AHTR may be intravascular or extravascular. Typically, haemolysis occurs within 24 hours of blood transfusion. Intravascular haemolysis mediated by ABO antibodies is the most dramatic and is potentially life-threatening if prompt treatment is not instituted. In ABO mismatch transfusion reactions, interaction of naturally occurring anti-A and anti-B with corresponding antigens in the recipient circulation provokes full complement activation. Membrane attack complexes (C5b- C9) are deposited on the red cell membranes, causing intravascular haemolysis. The degree of haemolysis depends on the site of haemolysis, class or subclass of the implicating antibody, volume of blood unit transfused and patient's clinical state [20]. It is most severe in the setting of an O recipient with high titre of anti-A and anti-B receiving A, B or AB blood unit. It is less severe when A red cells is given to B recipient or vice versa or where O plasma is infused into A, B, or AB recipient. The host

inflammatory response to the foreign antigen and the massive haemolysis underlies the symptomatology of AHTR. Affected patients may complain of pain/heat at the infusion site/cannulated vein, feeling of impending doom, chest tightness, loin pain or nausea [20]. The patient develops fever, associated with chills, rigors, tachycardia or hypotension which may progress to shock. Massive intravascular haemolysis may precipitate a pre-renal acute kidney injury (AKI). Release of pro-coagulant substances from red cell stroma may trigger activation of systemic intravascular coagulation, culminating in disseminated intravascular coagulopathy (DIC). Diagnosis of AHTR in an unconscious patient requires a high index of suspicion; the only pointers may be hypotension, haemoglobinuria or oozing from the infusion site. AHTR may mimic hyper-haemolytic crisis in sickle cell disease.

Treatment of AHTR is presented in Table 3 below [30,31,39,40].

4.3 Allergic Reactions

Allergic transfusion reactions are also common. It occurs in about 1–3% of all transfusions and is more

frequent in atopic individuals [41]. It is a type 1 hypersensitivity reactions mediated by IgE bound basophils and mast cells in previously sensitized blood recipients. When re-exposed to implicating allergens (most often plasma proteins) in the donor blood, antigen-antibody interaction causes cross-linking of bound immunoglobulins on mast cells, hence degranulation. Preformed vaso-active amines (principally histamine and serotonin) in mast cells and basophils are released [20,42]. As a late response, leukotrienes, slow release substances of anaphylaxis are also released. Typically, patient develops a localized or systemic urticarial rash with erythema and pruritus [29]. In severe allergies or anaphylactic reactions, other organs systems such as the chest, cardiovascular and gastro-intestinal are involved. Generally, allergies are more troublesome than dangerous. Allergies do not always recur in subsequent transfusions and is not associated with fever. Treatment modalities include temporary cessation of blood transfusion, relief of allergy and completion of transfusion after symptoms

abate. For control of symptoms, H-1 blocking antihistamines such as diphenhydramine 25–50 mg IV or oral should be administered. Newer antihistamines such as cetirizine and loratidine are less sedating. H2 blocking antihistamines may speed up resolution of symptoms. Transfusion should be resumed after 30 minutes if symptoms abate. In severe allergies or refractory cases, transfusion of the index blood unit should be stopped completely. In patients with laryngeal/facial oedema or even hypotension, adrenaline (subcutaneous) at 0.2–0.5 ml (1:1000 dilution 0.2–0.5 mg) should be administered [29]. For subsequent transfusions, pre-medications with antihistamines are recommended. Saline washed red cells is indicated in subsequent transfusion of patients with two or more serious allergic reactions that were unresponsive to H1 and H2 blockers. Incidence of allergic reactions is not reduced by leucocyte reduction [43].

4.4 Anaphylactic/Anaphylactoid Reactions

Anaphylactic reaction is a severe of allergy mediated by Ig E antibodies which induce cross linking of basophils and mast cells on reexposure to the allergens in the donor blood unit. Besides preformed mediators including serotonin and histamine, newly synthesized chemical mediators such as platelet activating factors (PAF), prostaglandins and leukotrienes are also released. PAF is believed to play a major/central role in anaphylaxis. PAF induces up-regulation of nitric oxide production, leading to widespread vessel dilatation and shock [29].

Anaphylactoid reactions are not mediated by Ig E antibodies. The classic anaphylactoid transfusion reaction occurs in the setting of an Ig A deficient blood recipient transfused with Ig A containing blood component.

Table 3. Treatment of acute haemolytic transfusion reaction

1. AHTR is suspected in a patient with transfusion-related fever which may be associated with loin pains/tachycardia/hypotension, drop in haemoglobin level within 24 hours of transfusion and evidence of haemolysis (elevated serum bilirubin, LDH and low haptoglobin levels).
2. AHTR is a haematologic emergency and should be treated as such.
3. Blood transfusion must be stopped immediately, while intravenous access is maintained with isotonic saline using a new infusion giving set. The patient's identity, blood bag label and compatibility form must be re-checked for any form of mismatch or clerical errors.
4. The discontinued blood unit, along with its tubing and the patient's post-transfusion blood sample should be sent to the blood bank. Repeat grouping with cross-matching must be performed on patient's pre- and post-transfusion samples. A direct anti-globulin test is usually positive.
5. Urine should be examined for haemoglobinuria. Blood chemistries including renal function test (serum electrolytes, urea and creatinine), markers of haemolysis such as serum bilirubin levels, LDH and haptoglobin levels, should be performed.
6. Patient's blood sample and the blood in the bag should be sent for microbiologic culture.
7. In suspected DIC cases, it is necessary to do coagulation studies including prothrombin time, activated partial thromboplastin time, thrombin time and plasma fibrinogen levels, D-dimers or FDPs. A full blood count may reveal neutrophilia, thrombocytopenia (in consumptive coagulopathy) and anaemia.
8. Patients with organ system damages such shock, renal shut-down should be co-managed with appropriate specialist teams in the intensive care units (ICU) or high dependency units.

9. Other supportive cares include adequate hydration to maintain normal blood pressure and good urinary output (at least 1 ml/kg/hr or 100 ml/hour).
10. If patient is oliguric, renal challenge with furosemide 40–80 mg IV stat (1–2 mg/kg in children) is given, with later doses adjusted to maintain adequate urine output. Dialysis is necessary if oliguria persists after 2 to 3 hours of renal challenge, further fluid and furosemide therapy may be contra-indicated.
11. Oxygen therapy should be administered if indicated. Antipyretics are given to control the fever.
12. Hypotension should be controlled with dopamine infusion 2–5 ug/kg/min. Other pressor drugs such as adrenaline, nor-adrenaline and high dose dopamine should be avoided since they reduce renal perfusion.
13. For an established DIC, replacement therapy should be offered. Fresh frozen plasma (FFP) at a dose of 10–15 ml/kg should be infused if PT or APTT ratio exceeds 1.5. Similarly, 1.5 Unit per 10 kg of cryoprecipitate is given if plasma fibrinogen level is less than 1 g/l. An adult therapeutic dose of platelet concentrate is given if counts drop below 50,000/ul.
14. Close monitoring of the patient's coagulation profile is necessary until the disease wanes.
15. Patient's haemoglobin level should be optimized with group identical blood units.

It is a rare entity. Ig A deficiency occurs with a frequency of about 1 per 700 persons [44]. However, most affected persons do not develop anti-Ig A. For individuals who develop anti-Ig A antibodies, upon transfusion of an Ig A containing blood component, Ig A anti-Ig A complexes are formed which trigger classical complement

pathways, inducing massive release of anaphylatoxins, C3a, C4a and C5a. There is massive dilatation of peripheral vessels, increased vascular permeability and pooling of blood in the peripheral, culminating in shock (cardiovascular collapse) [20,29,42]. Typically, the onset of symptoms occurs rapidly within seconds and minutes

of transfusion and multiple systems are involved including cutaneous, respiratory, cardio-vascular and gastro-intestinal manifestations [29,42]. The patient develops rapid onset of laryngeal oedema and bronchospasm with stridor, wheezing, coughing and respiratory distress. Other symptoms include generalized urticarial, erythema, tachycardia, hypotension, nausea, vomiting, diarrhoea, cramping abdominal or pelvic pain [42,45]. Severe reactions lead to shock, syncope, respiratory failure and death. Anaphylaxis is an emergency and should be managed by experienced staff in an ICU setting. Subcutaneous dose of 0.2–0.5 ml of 1:1000 epinephrine solutions (1 mg/ml) should be administered in adults (0.01 ml/kg body weight in children). This may be repeated every 15–30 minutes as needed. Further infusion may be titrated based on Blood Pressure. If systolic blood pressure drops below 60mmhg, IV epinephrine is given at a dose of 1–5 ml of a 1:10000 solution (0.1 mg/ml) in adults and 0.1 ml/kg IV push in children, over 2–5 minutes. A central venous pressure

(CVP) line may be used to monitor the effectiveness of fluid replacement and pressor infusion. For respiratory distress, supplemental oxygen at 4 Litres/min is given in adults [29]. Endotracheal intubation is given in laryngeal oedema with obstruction (stridor is a sign of laryngeal oedema). Endotracheal intubation with mechanical ventilation is instituted if $\text{PaCO}_2 > 65$ mmHg. If intubation is difficult or impossible, cricothyrotomy or tracheostomy is indicated. Wheezing is controlled with nebulized albuterol and IV aminophylline [29,42]. Urticaria/angioedema/GI distress is managed with an antihistamine, diphenhydramine 50 mg IV (in children 1–2 mg/kg IV). Intravenous hydrocortisone 200 mg 6 hourly is given to control late inflammatory responses. For subsequent transfusions, washed red cells are given. If plasma transfusions are needed, IgA deficient plasma must be administered [29,42].

4.5 Transfusion Related Acute Lung Injury (TRALI)

TRALI is defined as a new acute lung injury that develops with a clear

temporal relationship to transfusion in patients without alternate risk factors for acute lung injury [46]. TRALI is noncardiogenic, rare and is associated with infusion of plasma containing blood components. Transfusion related acute lung injury (TRALI) is a rare complication of blood transfusion. Its incidence is about 1 in 5,000–10,000 transfusions. It is a leading cause of transfusion related fatality [47]. It occurs more frequently in the setting of blood donations from multiparous women. Its aetiology is attended by the presence of leucoagglutinins in donor blood, causing agglutination of leucocytes (often times, that of the recipients, less frequently donor leucocytes or both) in the recipient pulmonary microcirculation. The resultant endothelial and epithelial injury, alveolar damage and inflammatory changes cause adult respiratory distress (ARD) like symptoms [48]. Most cases are mild-moderate and may be missed. Typically, the patients develops respiratory distress, associated with fever, chills, cough, usually within two hours of transfusion, but

sometimes up to 6 hours. Chest radiography shows new bilateral pulmonary infiltrates. There may be associated hypotension. Treatment essentially is supportive and patients may require high dependency unit (HDU) care [48]. Supportive therapy includes antipyretics and oxygen support [48]. Mortality rate is about 5 to 10% and most cases resolve within 72 to 96 hours [49]. TRALI is not improved by diuretic therapy. Transfusion of blood units from male donors reduces the risk.

4.6 Septic Transfusion Reaction

Septic transfusion reaction (STR) is a potentially life-threatening complication that results from bacterial contamination of a blood unit. Bacterial contamination may be due to asymptomatic bacteraemia in the donor or contamination by skin commensals during the blood collection process [50]. STR is commoner with platelet transfusion than red cell transfusions due to room temperature storage of platelets [41]. Psychrophilic organisms such as *Yersinia enterocolitica*, is associated with red cell contamination. Commonly implicated

organisms in platelet transfusions include *Staphylococcus aureus*, coagulase negative staphylococci, diphtheroids and other skin commensals [50,51]. Depending on species and load of the implicating bacteria in the blood component, the patient develops fever (usually above 39°C) with chills and rigors, tachycardia, hypotension, dyspnoea, gastro-intestinal tract disturbances and may progress to DIC. Symptoms usually evolve during the transfusion process, usually within the first 15 minutes.

In cases of suspected acute transfusion reaction due to bacterial contamination, the blood unit should be stopped immediately. The blood bank should be notified immediately so that other components from same donor can be traced and withdrawn before use. Microbiologic testing should be commenced immediately. Samples for blood culture should be taken from the blood unit and the patient and sent for appropriate testings [52]. Treatment involves commencement of broad spectrum antibiotics before culture results are made available. Patient should be monitored closely

with aggressive supportive care for fever, shock and DIC as indicated [45].

STR can be prevented by applying measures that reduce or eliminate bacterial contamination of blood components. Proper donor arm cleansing and diversion of the first 20–30 mls of blood reduces the risk of bacterial contamination by up to 77% [53–55]. Donated units should intermittently be checked and cultured for bacterial contamination. Visual checks of every blood unit should be performed before transfusion [52]. Visible growth in the bag, flocculation and discoloration are signs of bacterial contamination. Storage of platelet units should not exceed 5 days except in settings where bacterial detection systems are available and monitoring/bacterial culture is performed between days 2 and 3 [52,56].

4.7 Transfusion Associated Circulatory Overload

Transfusion associated circulatory overload (TACO) is a potentially fatal complication, with incidence of about 0.1 to 1% of all transfusions. Neonates, elderly patients, patients with cardiac or renal disease

are at particular risk. TACO is caused by pulmonary oedema induced by volume overload during large volume transfusions or infusion of blood products with high osmotic load. Clinical features of TACO include cough, dyspnoea, raised jugular venous pressure (JVP), bibasal crepitations, tachycardia, hypertension and widened pulse pressure [41]. Elevated Brain Natriuretic peptide, BNP, a peptide secreted from the ventricles in response to increased filling pressures, may assist in diagnosis [57]. In patients with TACO, transfusion should be discontinued immediately and treatment for heart failure commenced. Typically, furosemide 20–40 mg IV is given and patient is nursed with cardiac position. Oxygen therapy may also be required.

In at risk patients, transfusion should be administered at a slower pace at longer intervals except in emergencies. Premedication with a diuretic, furosemide 20–40 mg IV stat should be given. For patient requiring immediate reversal of warfarin overdose, prothrombin complex

concentrate (PCC) is preferred to infusion of large volumes of FFP. Packed red cells or red cell concentrate is the appropriate component.

4.8 Complications of Massive Blood Transfusion

Massive blood transfusion is said to occur when a blood recipient has received at least one blood volume within a 24 hours period. This is often associated with conditions of acute blood loss following trauma or obstetric complications. With replacement of one blood volume, dilutional coagulopathy sets. With replacement of 1.5 times blood volume, dilutional thrombocytopenia set in. Complications of massive blood transfusion are related to biochemical and metabolic changes that accompany blood storage, as well as dilutional effects of large volume transfusion. They include metabolic and coagulopathic complications. Metabolic complications include citrate toxicity with resultant hypocalcaemia, hyperkalaemia and hypothermia [40]. Symptomatic hypocalcaemia manifests as perioral tingling, facial numbness,

muscle twitching and cardiac arrhythmias in extreme cases. With prolonged storage of red cells, intracellular potassium leaks out of the cells into the suspending plasma, hence hyperkalaemia. This is particularly significant in neonates receiving EBT with stored blood or patients with renal disease. Most anticoagulants in routine use are citrate based and they act by chelating calcium ions. Infusion of large volumes of citrated plasma induces hypocalcaemia. Blood is stored at 2– 6°C. Transfusion of several cold units of blood induces hypothermia and increases risk for cardiac arrest and DIC. Massive transfusion is associated with clotting abnormalities from dilutional effects, attended by hypothermia. In current practice, an expectant approach often denoted as massive transfusion protocol is usually engaged in massive transfusion [14,58]. Treatment guideline depicted in Table 4 below is recommended in patients enduring massive blood transfusion.

5. DELAYED/LONG-TERM COMPLICATIONS AND TREATMENT GUIDELINES

5.1 Delayed Haemolytic Transfusion Reactions

Delayed haemolytic transfusion reactions (DHTR) may be secondary or primary. Secondary forms occur in individuals that have been previously sensitized during prior transfusion or pregnancies but have low (undetectable) antibody titre which was missed during routine compatibility testings. However, upon re-exposure to the antigens during transfusion, there is a brisk anamnestic response with production of high titre Ig G allo-antibodies. Delayed haemolysis ensues and may occur up to 1 to 2 weeks post transfusion. Primary forms occur without prior antigenic sensitization and occurs up to 28 days. DHTRs are mediated by Ig G antibodies. Rh, Kell and Kidd antibodies are frequently implicated. DHTRs are often missed since most patients are often asymptomatic or may develop slight fever. In the absence of clinical evidence and only serologic confirmation, the term Delayed serologic transfusion reaction (DSTR)

is used. As such, the actual incidence may be difficult to estimate. Some authors put its incidence at about 1 in 1500 transfusions [60,61]. The clinical suspicion of DHTR may be raised by a triad of fever, hyperbilirubinaemia (jaundice) and drop in post-transfusion haemoglobin levels. Diagnosis is confirmed by a positive posttransfusion DAT. Significant DHTRs are treated in a similar form to AHTRs. DHTR is not totally preventable or predictable. However, it is recommended that fresh serum samples should be used for pre-compatibility testing if last transfusion occurred more than 72 hours [20].

5.2 Red Cell Allo-immunisation

Allo-immunization is a potentially fatal immunologic disease characterized by development of allo-antibodies against non-self antigens following exposure through transfusion, pregnancy, deliberate injection of immunogenic materials or transplant [62]. Clinical sequelae of red cell allo-immunisation may include delayed haemolytic transfusion reaction, acute haemolytic transfusion reaction and haemolytic disease of the fetus and newborn [63,64].

Table 4. Massive transfusion protocol (MTP)

1. There must be a clear trigger for activation of an MTP. This presupposes that every transfusion service/unit should develop appropriate guidelines and protocols.
2. There should be a single person/co-ordinator saddled with the responsibility of establishing continuous communication and collaboration between the blood bank, clinical unit and other requisite services.
3. A porter/runner should be designated for prompt transfer of blood components and samples when necessary.
4. Targets include an haemoglobin level of 10 g/dl, prothromin time ratio/APTT ratio of at most 1.5, platelet count in excess of 50,000/ul (100,000/ul in polytrauma/CNS trauma) and, plasma fibrinogen level greater than 1g/L. pH>7.2, base excess<6, lactate<4 mmol/l, ionized calcium>1.1 mmol/l should be maintained.

5. Monitoring of patient's full blood count and coagulation studies should be repeated every 3 to 6 hours and at every instance after infusion of plasma components.
6. Fresh frozen plasma should be given at 10–15 ml/kg if PT/APTT Ratio is greater than 1.5, or 1 blood volume (~10 units) has been replaced.
7. Cryoprecipitate is given at a dose of 1.5 unit/10kg if fibrinogen is less than 1 g/l.
8. Platelet concentrate is administered if counts are less than targets or after 1.5 times blood volume (~12 units) has been replaced.
9. Hypothermia (core temperature <35°C) must be counteracted. Blood and resuscitation fluids should be pre-warmed using temperature controlled blood warmers or warm air blankets. Warming blood to 33–35°C, not only prevents hypothermia, but also improve blood flow up to 50% by reducing viscosity [59].

Red cell allo-immunisation also accounts for difficulties in selecting appropriate antigen negative units for transfusion especially in the setting of multiple allo-antibodies. However, alloimmunisation rate is higher in patients with history of multiple transfusions or patients on chronic blood transfusion therapy such as thalassemia major and sickle cell disease [65–67]. In most developed centres worldwide (UK and US), routine allo-antibody screening of blood recipients and donated blood units or donors is carried out. This allows detection of atypical antibodies in potential blood recipients. Allo-antibody

screening if positive must be followed by antibody identification. When the specificity of the implicating antibody is known, the transfusion laboratory must ensure the selection and provision of antigen-negative blood units (or the least incompatible) for all future transfusions [20].

Incidence of erythrocyte allo-immunisation among at-risk patients may be reduced or prevented by a closer donor–recipient matching, especially in settings of multiple or chronic blood transfusions. Antenatal and postnatal Anti-D prophylaxis should be offered to Rh D negative mother carrying Rh D positive babies.

5.3 Platelet Allo-immunisation

Repeated transfusion places the recipients at risk of allo-antibody formation. Platelet alloimmunisation is most frequently associated with HLA antigens. Occasionally, platelet specific antibodies are implicated. The clinical sequela of platelet allo-immunisation is refractoriness to platelet transfusions. It is noteworthy that platelet refractoriness may also be due to non-immune causes such as fever, splenomegaly, sepsis, occult or obvious bleeding, DIC or ITP or certain drugs [25,68].

Platelet refractoriness is assessed with the corrected count increment (CCI). Non immune causes of platelet refractoriness are commonest and should be excluded in suspected cases. CCI is estimated using 15 minutes to 1 hour posttransfusion platelet count, patient's body surface area and the platelet yield. CCI less than 7.5 at 1 hour or less than 4.5 at 24 hours on at least two occasions is in keeping with platelet refractoriness [68–70]. In refractory patients suspected to be due to platelet alloimmunisation, platelet cross match is

needed to identify and provide compatible units. In the alternative, HLA matched platelet units should be transfused [25,68,69]. Such patients should be regularly monitored with CCI [68–70].

5.4 Post-transfusion Purpura

Post transfusion purpura (PTP) is a rare immunologic complication. It is thought to arise as a result of recipient allo-antibodies against platelet antigens, most commonly human platelet antigen (HPA) 1a and HPA 5b [71]. PTP is more common in multi-parous women due to sensitization from previous pregnancies. PTP occurs about 5 to 10 days after transfusion of red cells, platelets or plasma. Immunologic destruction of transfused platelets results in severe thrombocytopenia, manifesting as purpura. PTP should be suspected in patient presenting with purpura up to 12 days after transfusion. Diagnosis is confirmed by the presence of platelet allo-antibodies (usually anti-HPA 1a), detection of its antithetical antigen in the donor or by a positive platelet cross-match. In severe symptomatic cases,

treatment requires intravenous immunoglobulins or plasmapheresis as second option [41,72].

For subsequent transfusions, HPA-1a negative red cell or platelet component is preferable. If not available, a leucodepleted component should be given [20,41].

5.5 Transfusion Associated Graft vs Host Disease

Transfusion associated Graft vs Host disease (TA-GvHD) occurs up to about 1 to 6 weeks following blood transfusion. Its pathophysiology is consequent upon immune attack of host tissues (predominantly the liver, the skin, the gastro-intestinal tract) by immune-competent donor T lymphocytes [73]. Engraftment and proliferation of the foreign clone of T lymphocytes occur in the setting of an immune-compromised recipient or directed donation from a close relative with homozygous expression of HLA antigens for which the recipient is heterozygous. Other risk factors for TA-GvHD include bone marrow transplantation, intrauterine transfusion, congenital immunodeficiency states and HLA matched platelet transfusions [73–75].

Ta-GvHD should be

suspected in a patient presenting with fever, rash, diarrhoea, liver dysfunction, cytopenia, within 1 to 6 weeks of blood transfusion, for which no other apparent cause has been found. Diagnosis is confirmed by tissue biopsy of affected organs (Skin biopsy, liver biopsy or bone marrow aspiration) and genetic studies to show chimerism of both donor and recipient lymphocytes [74]. Though rare, Ta-GVHD is a dreaded complication, with very high mortality of over 90%, especially when diagnosis is delayed [74–76]. Treatment is largely supportive. TA-GvHD is unresponsive to immunosuppressive therapy. Leucodepletion does not eliminate the risk of TA-GVHD. Prevention of TA-GVHD rests on irradiation of all cellular products at a minimum recommended dose of 25Gy for all high risk patients [73,77,78].

5.6 Transfusion Siderosis

One unit of red cell transfusion contains about 200 to 250 mg of elemental iron. There is no exact physiologic mechanism for excretion of excess iron from the body. Plasma iron levels and storage iron is regulated by hepcidin regulated release of enterocytes and

iron laden macrophages. Daily body iron requirement vary by age, sex and other related conditions such as pregnancy. In an average adult, about 1–3 mg of iron is required daily [79]. Iron losses occur through sloughing off of skin and other epithelial surfaces and menstruation in females. As such, patients receiving multiple transfusions or chronic transfusions are at particular risk of iron overload [80]. Patients with conditions associated with some form of transfusion dependence such as myelodysplastic syndrome, aplastic anaemia, refractory anaemia, myelofibrosis are at particular risk of transfusional iron overload. Such patients should be closely monitored. Serum ferritin level gives a reflection of iron stores. However, serum ferritin level is falsely elevated in chronic inflammatory states such as infections and cancers, pregnancy and surgery and should be interpreted cautiously. Normal serum ferritin levels is about 15–300 ug/l. most authorities recommend commencement of iron chelation therapy when ferritin level is in excess

of 1000 ng/ml. a patient that has received about 20 to 30 units of red cells (equivalent to about 4 –6 gm of iron) is likely to be iron overloaded. Definitive diagnosis is liver biopsy. Liver iron in excess of 7 mg/g in adults and 4 mg/g in children is confirmatory [80,81]. Non-invasive evaluation using sequential quantum interference device (SQUID) is also reliable but relatively unavailable [82–84].

Iron overload induces tissue damage in major organs such as the liver, heart and endocrine glands. Such patients may present with liver cirrhosis with risk of transformation to hepatocellular carcinoma, cardiomyopathy, skin hyperpigmentation (bronze diabetes), diabetes mellitus, hypothyroidism, hypogonadism and other endocrine dysfunctions. Therapy requires iron chelation. Traditionally, intravenous desferrioxamine is used; however newer oral agents such as deferasirox (exjade, asunra) are currently available [85].

5.7 Transfusion Transmissible Infections

In developed areas of the world (UK and US), the risk of TTIs is very low or

perhaps negligible due to development of sophisticated testings for infectious pathogens (such as Nucleic Acid Testing, NAT), strict adherence to donor selection criteria and pathogen inactivation techniques [86–89]. In Nigeria and other sub-Saharan African countries, significant infectious risk is still associated with blood transfusion [90–94].

TTIs may be bacterial, viral or parasitic. Bacterial contamination of blood components has been discussed earlier. Known transfusion transmissible viral infections include Hepatitis viruses, HIV, HTLV-1 and HTLV-2 [13]. Parasitic infections such as *Plasmodium* spp, *Babesia* spp, *Leishmania* spp, *Trypanosoma* spp, *Toxoplasma* spp, and *microfilaria* are also transmissible through blood transfusions. Emerging pathogens, particularly viruses such as SEN V virus, Hepatitis G virus, West Nile Virus, human Herpes Virus – 8 (HHV-8) have also been described [95]. There is also a risk for transmission of prion diseases through blood transfusion [96,97]. However, for economic reasons, all known viral, bacterial or

parasitic agents are not routinely tested in blood donors, particularly in developing countries. However, most countries have minimum standard (mandatory screening) measures which often depend on the regional burden/prevalence of these infectious agents (epidemiological patterns), availability of requisite technology and cost of blood supply. As a counter measure (for prion diseases), all fractionated pooled plasma products used in the UK are sourced outside UK (from the US) since 1999 [20].

5.8 Mistransfusions/ Overtransfusion/ Under-transfusion

The term, ‘mistransfusion’ implies transfusion of a unit of blood to the wrong recipient and is often due to mis-identification errors. In the SHOT haemovigilance system, the category termed, ‘incorrect blood component transfused’ compasses both cases of mistransfusions and inappropriate blood use [12].

Over-transfusion refers to a practice where blood components are transfused in excess of patients estimated transfusion needs [98]. Whereas, under-transfusion is when blood in

transfused in a volume less than required to meet to physiologic needs. Under-transfusion may be associated with some benefits including lower risk of TTI, reduced incidence of acute transfusion reactions and less cost to the patient [98].

6. RECOMMENDATIONS

Strategies to improve blood transfusion safety as recommended by WHO include a well organised blood transfusion services, prioritization of blood donation from VNRBDs, screening of donated blood for at least the four major TTIs with quality assured system, rational use of blood and implementation of effective quality control systems [99].

Authors recommend that hospital transfusion committees should design and implement well designed protocols for management of transfusion reactions. These protocols should be distributed to all transfusion units in the hospital and should be updated regularly. As well, medical and nurse practitioners as well as blood bank staff should undergo regular training and retraining of diagnosis and treatment of complications of blood transfusion.

Autotransfusion as well as other alternatives to allogeneic transfusion should be explored where necessary. It is recommended that hospital blood banks should have a system for reporting suspected transfusion reactions. This should be carried out in consonance with the regional and national haemo-vigilance system to ensure adequate co-ordination.

7. CONCLUSION

The complications of blood transfusion are myriad. Good clinical practice is found on morally right and sound ethical principles of autonomy, beneficence, non-maleficence and justice [100]. Therefore, ensuring safe blood transfusions in healthcare systems remains an onus, not an option. Safety of blood transfusions in every transfusion service must be pursued and ensured by relevant stakeholders particularly those in developing nations. Blood systems in developing nations such as Nigeria should be upgraded to meet international standards.

Furthermore, there is need for development of local / institutional protocols and guidelines for management of complications of blood

transfusion in Nigeria, especially protocols for investigation and management of acute transfusion reactions. Such protocols should reflect best current practices, should be clear and readily accessible. All clinical staff involved in patient care should undergo training and retraining in relevant clinical areas of transfusion medicine. Improved awareness and knowledge regarding transfusion reactions is a critical step and leverage for successful implementation of institutional, regional and national haemovigilance systems.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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