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Review Article

Blood Transfusion and Complications

Emad Abdullah Subahi[1]*, Ibrahim Abdullah Abalhassan[2], Sarah Saud Abdulaziz Alsalem[3], Ahmed Nawaf Ahmed Al-Saleh[4], Sultan Sameer Alhunbusi[5], Mohammad Ibrahim Faya Assiri[6], Hassan Ali Hassan Al Gazwi[7], Murtaga Jafar Abdullah Makki[8], Walaa Sharif Osman Abdelrahman[9], Maram Abed Mabrook Alaiafi[6] and Eradah Ali Almarhoon[10]

[1]*Emergency Medicine Consultant, DESC, France, Al-Noor Specialist Hospital, Mecca, Saudi Arabia*

[2]*Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia*

[3]*Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia*

[4]*Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia*

[5]*King Abdul Aziz Specialist Hospital, Taif, Saudi Arabia*

[6]*King khalid University, Abha, Saudi Arabia*

[7]*Ras Tanura General Hospital, Eastern Province, Saudi Arabia*

[8]*Dammam Medical Complex, Eastern Province, Saudi Arabia*

[9]*University of Bahri, Sudan,*

[10]*Almaarefa College, Riyadh, Saudi Arabia*

***Corresponding Author:** Emad Abdullah Subahi, Emergency Medicine Consultant, DESC, France, Al-Noor Specialist Hospital, Mecca, Saudi Arabia.

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Abstract

Introduction: A side reaction or adverse event is known as the development of an undesirable unexpected effect or response in a patient following the administration of blood or any blood component. In current practice, even within developed countries, the highest risk to the patient is considered to be the non-infectious adverse events following transfusions that are responsible for a significantly high morbidity and mortality rates. In this review, the non-infectious complications which are related to blood transfusions were defined as non-infectious adverse transfusion reactions (NIATRs). The American Association of Blood Banks technical manual suggests guidance for the detection, diagnosis, management and grouping of non-infectious transfusion reactions, that could serve as a ready reference for physicians and other related health providers who deal continuously with blood transfusion. The acute and late non-infectious adverse transfusion reactions are categorized based on time of occurrence and later subdivided according to supposed etiology into immune-mediated subtype and non-immune mediated subtype.

Aim of Work: In this review, we will discuss blood transfusion and complications

Methodology: We did a systematic search for Blood transfusion and complications using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

Conclusions: Acute transfusion reactions are generally responsible for causing many serious side effects and complications. Awareness about various clinical manifestations and characteristics of acute transfusion reactions with the ability to evaluate the serious complications on a timely manner could lead to a better prognosis. Observation and strict monitoring are essential throughout the blood transfusion period, especially within the first fifteen minutes. There must be a standard operating procedure that contains the details for documentation, reporting, evaluation, and follow-up of all side effects and complications. Evidence based protocols of Restrictive strategy" or "Conservative approach" of blood transfusion to decrease the rate of unwanted blood transfusions has led to a significant improvements in current clinical practice.

Keywords: *Blood Transfusion; Complications; Non-Infectious*

Introduction

A side reaction or adverse event is known as the development of an undesirable unexpected effect or response in a patient following the administration of blood or any blood component [1]. In current practice, even within developed countries, the highest risk to the patient is considered to be the non-infectious adverse events following transfusions that are responsible for a significantly high morbidity and mortality rates [2]. In this review, the non-infectious complications which are related to blood transfusions were defined as non-infectious adverse transfusion reactions (NIATRs). The American Association of Blood Banks technical manual suggests guidance for the detection, diagnosis, management and grouping of non-infectious transfusion reactions, that could serve as a ready reference for physicians and other related health providers who deal continuously with blood transfusion [3]. The acute and late non-infectious adverse transfusion reactions are categorized based on time of occurrence and later subdivided according to supposed etiology into immune-mediated subtype and non-immune mediated subtype. A summary of several common non-infectious adverse transfusion reactions comprising the categorization, pathology, clinical manifestations, and treatment will also be provided in this review.

Methodology

We did a systematic search for Blood transfusion and complications using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: blood transfusion, complications, non-infectious.

Acute non-infectious blood transfusion

Adverse reactions

Developing within twenty-four hours following blood transfusion, adverse reactions are categorized into Acute immune mediated blood transfusion reactions and Acute Non-immune mediated - blood transfusion reactions. Acute immune mediated - blood transfusion reactions are later sub-classified into several subtypes.

Acute hemolytic transfusion reactions

A hemolytic transfusion reaction is a reaction where clinical manifestations or laboratory investigations show higher rates of destruction of red blood cells which is caused by the blood transfusion. In acute hemolytic transfusion reactions (AHTRs) clinical manifestations start to appear within few minutes following the initiation of the blood transfusion. Common laboratory characteristics include hemoglobinemia, hemoglobinuria, reduced serum haptoglobin concentrations, unconjugated hyperbilirubinemia, elevated Lactate dehydrogenase and serum glutamic-oxaloacetic transaminase concentrations and reduced hemoglobin. The interaction of recipient's produced antibodies with donor's red cell antigens causing immediate destruction of the transfused red blood cells is the immunologic underlying mechanism for acute hemolytic transfusion reactions.

Rarely, blood transfusion of ABO-incompatible plasma (like ABO mismatch platelet transfusion) might lead to hemolysis of the patient's red blood cells specifically if donors have high levels of ABO antibodies. acute hemolytic transfusion reactions and associated mortality have been observed to happen at approximately one in 76,000 and one in 1.8 million units transfused, respectively. recommendations for the detection and management accordingly for acute transfusion reactions, adapted from the world health organization guidelines use of blood during surgery and anesthesia had been proposed [4].

Febrile nonhaemolytic transfusion reactions

Febrile non-hemolytic transfusion reactions (FNHTRs) are generally characterized by the presence of an otherwise unexplained elevation in body temperature of at least 1°C during or soon following blood transfusion. Anti-pyretic pre-medications might lead to masking the fever, but they do not often prevent the development of chills and/or rigors, that are caused by cytokine mediated systemic

inflammatory response. Other causes of fever must be ruled out before confirming a diagnosis of Febrile non-hemolytic transfusion reactions. Febrile non-hemolytic transfusion reactions are generally seen more frequently following platelets transfusion (up to thirty percent of cases of platelet transfusion) than red blood cells as platelets are stored at room temperature, which increases activation of leucocytes and accumulation of cytokines [5]. Treatment of Febrile non-hemolytic transfusion reactions is usually symptomatic.

The pre-storage laboratory leuco-reduction is beneficial and is higher effective than bedside leuco-reduction. Allergic reactions clinical manifestations might either happen within seconds or minutes following the initiation of transfusion or might take several hours before it develops.

Urticaria

Urticaria is considered to be the mildest type of allergic reactions that occur abruptly, often leads to itching and could last for few hours or up to few days before starting to disappear. More severe cases might be accompanied by the development of angioedema. The incidence of urticaria is one-to-three percent of blood transfusions [6]. Once clinical manifestations subside, the transfusion might be completed. Severe complications might be treated with methylprednisolone (125 mg IV) or prednisone (50 mg orally).

Anaphylaxis

Anaphylaxis is considered to be a more severe type of allergic reactions that has an incidence of 1: 20,000 - 1:50,000 of all blood transfusions [7] where severe decreased of blood pressure, shock, and loss of consciousness could happen [8]. Anaphylaxis adverse event is frequently observed in IgA deficient recipients where it is a result of antibodies against donor IgA. Patient antibodies against haptoglobin penicillin, the C4 determinant of complement and ethylene oxide have all been found as the causation. The terminology 'anaphylactoid' is generally used for reactions with clinical manifestations which are similar to anaphylaxis but are not mediated by IgE. If the patient lost consciousness or in shock, injected IV adrenaline might be given along with strict cardiac monitoring [9].

Transfusion related acute lung injury

Transfusion related acute lung injury (TRALI) is a subtype of acute lung injury (ALI) and is a main cause of transfusion-related morbidity and mortality. Transfusion related acute lung injury has been known as having:

- Acute injury of the lung with having hypoxemia and PaO_2/FiO_2 that is less than 300 or SpO_2 that is less than ninety percent on room air.
- Bilateral pulmonary edema seen on frontal chest radiograph.
- absence of evidence of left atrial hypertension.
- absence of preexisting acute lung injury prior to transfusion.
- Onset of clinical manifestations is within six hours of transfusion.
- No temporal relationship to an alternative risk factor for acute lung injury.

Possible Transfusion related acute lung injury is also defined with the same criteria as for Transfusion related acute lung injury, but, in the setting of an alternative risk factor for acute lung injury. The lung injury in Transfusion related acute lung injury is most frequently temporary, and about eighty percent of patients will recover within forty-eight to ninety-six hours.

In contrast to Transfusion associated circulatory overload (TACO), pulmonary edema in Transfusion related acute lung injury is non-cardiogenic and does not improve using diuretic treatment. Transfusion related acute lung injury is a clinical diagnosis; laboratory investigations is only used to support the diagnosis. Transfusion related acute lung injury is the new onset or deterioration of pulmonary functions with hypoxemia that meets the international criteria for acute lung injury (PaO_2/FiO_2 less than 300 mmHg), with a chest X-ray consistent with pulmonary edema happening during transfusion itself or within six hours following the transfusion [10]. All plasma-containing components, like whole blood, red blood cells, platelets, cryoprecipitate and fresh frozen plasma, have been implicated in Transfusion related acute lung injury. The occurrence of Transfusion related acute lung injury has been estimated to be about one

in every five thousand blood component transfusions. Antibodies can be produced against leucocytes (polymorphous neutrophil [PMN]), both for neutrophils and human leucocyte antigen following the exposure to foreign antigens via pregnancy, transfusion, or transplantation. Two different etiologies have been suggested. It could be a single antibody-mediated event that involves the transfusion of anti-human leukocyte antigen (HLA) or anti-granulocyte antibodies into patients who have leukocytes express the cognate antigens. In most cases with antibodies, the source of antibodies is the donor, rather than patient. A two-event model of the mechanism of Transfusion related acute lung injury has also been suggested causing neutrophil activation leading to damage of the pulmonary endothelial tissue, capillary leakage, and/or pulmonary edema. Following prompt respiratory support significant clinical recovery can occur within two to four days [11].

Following updated transfusion guidelines might reduce rates of unnecessary transfusions and its related morbidity. additionally, many investigators, transfusion medicine professionals, and the American Association of Blood Banks advises temporary disqualification of donors who are implicated in Transfusion related acute lung injury reactions until leucocyte antibody assessment is performed. If these donors are found to have antibodies to high-frequency leucocyte antigens, they must be disqualified from plasma donation or platelet donation.

To make the blood donation safer, the United Kingdom has disqualified all multiparous women from plasma donation due to the possibility that plasma from these women might be a significant factor in Transfusion related acute lung injury. For elective major surgical procedures that require blood transfusions, washing of cellular components removes antibodies, lipids and/or other biologic response modifier from the plasma fraction. Using packed red blood cells (PRBCs) for less than fourteen days and platelet concentrates for less than two days might avert many of the effects of these compounds, that accumulate during storage as there is no significant accumulation of PMN priming activity during shorter storage times for packed red blood cells and platelet levels, respectively.

For later considerations, patients who are at a higher risk for developing Transfusion related acute lung injury might include therapies such as anti-platelet agents and alternatives to traditional blood components such as prothrombin complex concentrates [12].

Management of transfusion related acute lung injury

Management is usually supportive. Effective treatments for reducing the occurrence of Transfusion related acute lung injury include the use of only men's plasma and apheresis platelets. Better understanding of the blood component and patients' predisposing factors for Transfusion related acute lung injury could likely result in significant treatment and prophylactic protocols for decreasing the incidence of this life-threatening syndrome. Transfusion related acute lung injury treatment consists mainly of preventing the development of future complications and reactions. A patient where Transfusion related acute lung injury is suspected must be reported to the National Blood Bank for a serological workup of the recipient and the implicated donors on the presence of HLA and HNA antibodies.

Incompatibility is assessed by cross-matching donor plasma against recipient's leucocytes. A donor with antibodies that are not compatible with the patient is ruled out from later donation of blood for transfusion products.

Acute non-immune mediated adverse reactions

Transfusion related sepsis

Despite being not relatively common, transfusion-related sepsis can be a fatal complication. The diagnosis of transfusion-related sepsis is usually based on the presence of at least one of the clinical characteristics: (1) fever that is higher than 39°C (102°F) or increase of more than 2°C (3.5°F); (2) increase in the heart rate that is higher than 120 per minute, or an increase of more than 40 per min); (3) shaking chills and (4) a change in the systolic blood pressure that is higher than thirty mmHg rise or a decrease in systolic blood pressure) within ninety minutes following blood transfusion. In more severe cases, the patient might get shock with associated kidney failure and disseminated intravascular coagulation (DIC).

Isolation of the same causative organism from the patient and the remainder of the blood bag is important in diagnosing the transfusion-related sepsis and differentiating it from AHTRs and FNHTRs. As platelets are stored at room temperature, they are considered to be more susceptible than red blood cells to bacterial contamination with a higher risk.

The chances of transfusion associated sepsis were found to be higher with random-donor platelet than with an apheresis unit. Broad spectrum antibiotics must be used for management of transfusion associated sepsis with other standard care treatment for sepsis. Screening of platelet units for bacterial contamination and adopting "diversion technique" during blood collection could reduce the risk. Besides the use of disinfectants, bacteria might be introduced into the blood container by methods of skin core when the blood collection needle enters the skin (this is seen in about sixty-five percent of all veno-punctures).

In diversion techniques, withdrawal of the initial fifteen-to-thirty mL of whole blood from the main container may cause decreased risk of bacterial contamination.

Non immune hemolytic reactions

Red cell hemolysis because of transfusion could also result from several nonimmune-mediated causes (also referred as pseudo-hemolysis) that might be temperature-related or mechanical; as an example, unideal storage temperature, bad use of blood warmer, the use of hot water baths and microwave ovens, the use of a needle with an inappropriately small bore size or using a rapid pressure infuser, infusion of red blood cells with same tubing with hypotonic solution or some pharmacologic agents. The treatment is generally the same as in the AHTRs.

Transfusion associated circulatory overload

Major morbidity and mortality is usually associated with transfusion-associated circulatory overload [13]. Patients at higher risk of Transfusion associated circulatory overload are relatively old patients, young infants, patients who have renal failure, having hypo-albuminemia, different types of anemia, congestive heart failure or fluid overload or the presence of a past history of plasma transfusion. Clinical signs and manifestations include dyspnea, orthopnea, cyanosis, higher heart rate, jugular venous distension, and pedal edema. Increased blood pressure that is characterized by a widening of the pulse pressure is characteristic. It is seen in less than one percent of transfused patients. Transfusion associated circulatory overload might lead to the development of acute pulmonary edema within six hours following the blood transfusion. Treatment is usually an optimization of the main etiology and mechanical ventilation, fluid restriction, administration of diuretics [14].

Transfusion associated dyspnea

It is defined as respiratory distress within twenty-four hours of blood transfusion that does not meet the criteria of Transfusion related acute lung injury, Transfusion associated circulatory overload or allergic reaction or other known etiologies.

Acute hypotensive transfusion reaction

This is known as the development of an abrupt and early drop in blood pressure with the lack of other causes of the decline in the blood pressure. therefore, it might happen as an isolated outcome, but it responds quickly to stopping the blood transfusion and applying symptomatic treatment [15]. Patients who have otherwise unexplained hypotensive blood transfusion complications must be administrated a trial of washed blood products. Bedside leuko-reduction filters have been used more usually in the settings of acute hypotensive transfusion reactions despite that it has also occurred with pre-storage leuco-filters.

Transfusion associated immunomodulation

The down-regulation of recipient's cellular immune response that is caused by allogeneic blood transfusion has classically been known as Transfusion associated immunomodulation (TRIM) [16]. The detrimental clinical manifestations of Transfusion associated immunomodulation are having higher risks of acquiring post-operative infections and malignancy recurrence and possibly a transfusion-related multiple organ dysfunction syndrome. Transfusion associated immunomodulation is thought to be mediated

by allogeneic leucocytes or their soluble products. One of the plausible pathophysiological mechanisms suggested for this is immune deviation towards T-helper lymphocytes type two cytokine characterized by the secretion of interleukin (IL-4), IL-5, IL-10 cytokines with decreased secretion of T-helper lymphocytes type one cytokines namely IL-2, IL-12, and interferon-γ. Use of autologous blood or pre-storage leuco-filtered blood could mitigate the adverse effects of Transfusion associated immunomodulation [17].

Transfusion-associated graft versus host disease

Transfusion-associated graft versus host disease (TA-GVHD) is a clinical syndrome that is characterized by the development of fever, maculopapular rash that progresses to hemorrhagic bullae, enterocolitis with watery diarrhea, abnormal liver function tests, pancytopenia and findings of characteristic histological appearances on biopsy that classically begin eight to ten days following blood transfusion.

Conclusions

Acute transfusion reactions are generally responsible for causing many serious side effects and complications. Awareness about various clinical manifestations and characteristics of acute transfusion reactions with the ability to evaluate the serious complications on a timely manner could lead to a better prognosis. Observation and strict monitoring are essential throughout the blood transfusion period, especially within the first fifteen minutes. There must be a standard operating procedure that contains the details for documentation, reporting, evaluation, and follow-up of all side effects and complications. Evidence based protocols of Restrictive strategy" or "Conservative approach" of blood transfusion to decrease the rate of unwanted blood transfusions has led to a significant improvements in current clinical practice.

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