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Case Series

Transfusion Medicine Section

Blood Transfusion Recipients with Alloantibodies of Anti C, c, E, e and Anti D+C (?G): A Series of 11 Cases

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ABSTRACT

The process whereby non ABO antibodies form after a Red Blood Cell (RBC) transfusion, pregnancy, or transplantation is known as alloimmunisation. The likelihood of developing alloimmunisation is influenced by factors such as transfusions, multiple pregnancies, underlying diseases, the cause of anaemia, and the recipient's immune response to the non-self RBC antigens they encounter. Alloantibodies can complicate crossmatch testing, leading to delays in securing compatible blood. Therefore, for a patient with a history of detectable clinically significant antibodies, donor units selected for transfusion must be negative for the corresponding antigen(s). In this context, the authors present a series of 11 cases (7males ,4 females) transfusion recipients and their characteristics for being at risk of alloimmunisation.

Keywords: Alloimmunisation, Crossmatching, Phenotyping

INTRODUCTION

The process whereby non ABO antibodies form after a RBC transfusion, pregnancy, or transplantation is known as alloimmunisation [1]. This occurs when someone without a specific antigen is exposed to it, leading to the production of non ABO antibodies. The likelihood of developing alloimmunisation varies among different patient groups and medical conditions. In healthy blood donors, the rate of alloimmunisation is below 0.3% [1]. For all transfusion recipients, this rate is about 2% to 5%. However, in patients who require frequent transfusions due to conditions like Sickle Cell Disease (SCD), myelodysplastic syndrome, thalassaemia, or autoimmune haemolytic disease, the rate of alloimmunisation can be 30% or higher [1].

The immune system's response to RBC proteins is generally not very robust, with the notable exception of the D antigen. Approximately 85% of healthy D-negative individuals exposed to the D antigen will develop anti D antibodies. In contrast, exposure to other antigens result in much lower rates of sensitisation: around 10% for anti-K in K-negative individuals, 7% for anti E, and 3% for anti c. The response to other minor blood group antigens is less than 3% in antigen-negative individuals. The likelihood of alloimmunisation is influenced by factors such as the number and frequency of transfusions, multiple pregnancies, the patient's underlying diseases, the cause of anaemia, and the recipient's immune response to the non-self RBC antigens they encounter. Additionally, differences in ethnic and antigenic patterns between donors and recipients have been noted to impact alloimmunisation rates [1].

Individuals who are more prone to developing RBC alloantibodies are referred to as responders. Within this group, some individuals develop multiple alloantibodies and are known as hyper-responders. Alloantibodies can complicate crossmatch testing, leading to delays in securing compatible blood. Ensuring transfusions that are antigen-matched can effectively prevent alloimmunisation. This requires typing the patient's ABO, Rhesus, Kell, Kidd, and Duffy systems either at diagnosis or before starting transfusion therapy [1,2]. The need to analyse patient profiles and risk factors among alloimmunised transfusion recipients is crucial for identifying high-risk groups, guiding personalised transfusion strategies to prevent complications such as haemolytic reactions. Additionally, it enhances blood bank policies, optimises donor matching, and provides region-specific insights into alloimmunisation patterns, thereby improving overall transfusion safety and efficacy.

CASE SERIES

In this study, 11 patients were identified with alloantibodies, including anti C, anti c, anti E, and anti D+C (?G). No patients were identified with anti e. Among these 11 alloimmunised patients, 7 (63.63%) were alloimmunised to the "E" antigen, 1 to the "c" antigen, 1 to the "C" antigen, and 2 had formed anti D+C (?anti-G). Of the total, 7 (63.63%) were men, and 6 (54.54%) were over 50 years of age. Additionally, 4 of the 11 alloimmunised patients (36.36%) had a diagnosis of suspected malignancy.

With respect to transfusion history, four patients had received an average of 1-5 units of Packed Red Blood Cells (PRBC), two had received an average of 10-15 units, two had received more than 30 units, and two had at least one transfusion with further details of transfusion unknown. A significant 90.90% were transfused PRBCs for anaemia, and 6 (54.54%) had a B positive blood group. There were no blood grouping discrepancies encountered in these cases, and only crossmatch compatible units were transfused for all cases.

Anti C: The patient with anti C antibody was a 66-year-old female with a history of anaemia of chronic disease and an unknown obstetric history. She had undergone bilateral knee replacements and received one unit of PRBC transfusion during surgery.

A 17-year-old male diagnosed with sickle cell anaemia was identified with anti c. He presented with complaints of fatigue, pallor, and anaemia. His medical history reveals that he has been a known case of SCD since being diagnosed at eight years old in an outside hospital. He has a history of episodes of fatigue and occasional abdominal and back pain due to vaso-occlusive crises, as well as over two episodes of acute chest syndrome, which were treated with hydration, intravenous antibiotics, and analgesics. The patient underwent a cholecystectomy at age eight. Upon recent admission, his haemoglobin was recorded at 6.2 g/dL, with a positive antibody screen and a negative direct Coombs test. A peripheral blood smear showed normocytic normochromic anaemia with anisocytosis and numerous sickle cells. His reticulocyte count was elevated at 11.87%, and ferritin levels were significantly high at 843.30 ng/mL (normal range: 30-400 ng/mL). His blood group is A positive and has been receiving regular transfusions every 2-4 weeks since 2015, with over 40 compatible units of PRBCs transfused. Since 2019, leukofiltered

packed red cells have been administered, and on average, six units had to be crossmatched to find one compatible unit. During subsequent admissions, c antigen-negative units were provided.

Anti E: In this study, seven patients were identified with anti E antibodies; 4 (57.14%) were male and 3 (42.85%) were over 50 years old, with three diagnosed with carcinoma. Among these cases, a 17-year-old male presented with complaints of pallor, anaemia, short stature, and delayed puberty. He is a known case of beta thalassaemia major, with severe iron overload and is on iron chelators. The patient underwent a splenectomy in 2012 and has been treated for Hepatitis C virus. His blood group is B positive, and upon recent admission, his haemoglobin was found to be 7.2 g/dL, with positive antibody screen and direct Coombs test results. Peripheral smear and reticulocyte counts were not available, and his ferritin level was significantly elevated at 6402.0 ng/mL. He has a borderline reactive HBsAg and has a history of receiving monthly transfusions with leukofiltered PRBCs, totalling more than 40 units, with only compatible units provided during these transfusions.

Anti D+C (?G): The two patients identified with anti D+C were males over 50 years old, diagnosed with coronary artery disease and carcinoma, and had Rh-negative blood groups. The demographic and clinical characteristics of the study patients have been presented in [Table/Fig-1].

Variables	Category	Frequency	Percentage
Age	10-20 years	2	18.18%
	21-30 years	1	9.09%
	31-40 years	1	9.09%
	41-50 years	1	9.09%
	>50 years	6	54.54%
Sex	Males	7	63.63%
	Females	4	36.36%
Disease condition	Carcinoma	4	36.36%
	Chronic kidney disease	1	9.09%
	Beta thalassaemia major	1	9.09%
	Sickle cell anaemia	1	9.09%
	Coronary artery disease	2	18.18%
	Iatrogenic	1	9.09%
	Anaemia of chronic disease	1	9.09%
Antibody identified	Anti E	7	63.63%
	Anti e	0	0%
	Anti C	1	9.09%
	Anti c	1	9.09%
	Anti D+ C(?G)	2	18.18%
Blood transfusion	1-5 units	4	36.36%
	10-15 units	2	18.18%
	>30 units	3	27.27%
	Unknown history	2	18.18%
Indication for transfusion	Anaemia	10	90.9%
	Haemorrhage	1	9.09%
Blood group	D antigen		
	Positive (%)	Negative (%)	
A	2 (11.1)	1 (9)	
B	6 (54.5)	1 (9)	
AB	0	0	
O	1 (9)	0	

[Table/Fig-1]: Demographic, clinical characteristics and probable triggers of the alloimmunised patients.

DISCUSSION

In this study, alloimmunisation to the E antigen was most frequently identified. Similar findings were reported by Bhuva DK et al., who observed a predominance of anti E alloimmunisation among patients with Rhesus antibodies other than anti D [2]. The most common alloantibody, as reported by Thakral B et al., was anti c (38.8%), followed by anti E (22.2%) [3]. Additionally, anti E alloantibody was the most frequently encountered alloantibody, according to Gupta R et al., and Elhence P et al., in multitransfused patients [4,5].

Adsorption and elution studies to distinguish anti D+C from anti-G were not performed, as they were not necessary for transfusion purposes; the patient would receive D-negative and C-negative blood regardless of whether the antibody is anti D, anti C, or anti-G. All units issued to patients in this study were crossmatch compatible, and no haemolytic transfusion reactions were noted. The diseases requiring the most transfusions included sickle cell anaemia, beta thalassaemia major, and chronic kidney disease. The highest risk of alloantibody formation was observed in recipients suspected of having malignancy who were in an immunosuppressed state post-chemotherapy. Since all patients with alloantibodies had a transfusion history, it seems that transfusion plays an important role as an alloimmunisation factor. None of the females alloimmunised in this study had a previous history of abortions.

For the case of the 17-year-old male patient with anti c antibodies diagnosed with sickle cell anaemia, an average of six units were crossmatched for one compatible unit. However, the prevalence of c antigen-negative donors in India is 41.9%, suggesting that only around three units should be crossmatched for one compatible unit [6].

Another 17-year-old patient with anti E antibodies, who was a known case of beta thalassaemia major, had all crossmatched units compatible, aligning with the 80% E antigen-negative Indian donor population [6]. In a systematic review by Franchini M et al., on red cell alloimmunisation in transfusion-dependent thalassaemia patients, key risk factors were identified as age, being female, undergoing splenectomy, receiving the first transfusion before the age of two, and the total number of RBC units received, as well as the duration and frequency of blood transfusions [7]. Abe M et al., proposed that genetic factors should also be considered [8].

Additionally, Singer ST et al., found that patients who had undergone splenectomy had higher alloimmunisation rates due to the absence of an efficient filtering system for removing damaged RBCs, potentially enhancing immune reactions [9]. In this study, one of the 11 alloimmunised patients had undergone splenectomy; however, the sample size was too small to establish a definitive relationship.

According to Jariwala K et al., the rate of alloimmunisation among SCD patients in India is reported to be 11%; however, this was not the focus of our study [10]. Additionally, Pahuja S and Mandal P found autoantibodies in patients who had undergone multiple transfusions, which were not observed in our study [11]. Hendrickson JE and Tormey CA explored the triggers of RBC alloimmunisation, emphasising the complex interplay between immune activation, patient-specific factors, and transfusion-related risks, similar to our study [12]. They discuss how certain individuals, particularly those with conditions like SCD and thalassaemia, are at higher risk due to frequent transfusions and genetic predispositions. The immunogenicity of specific RBC antigens and mismatches beyond the ABO/RhD system contributes significantly to antibody formation, complicating future transfusions and increasing the risk of haemolytic reactions. The authors highlight the need for extended antigen matching and personalised transfusion strategies to mitigate alloimmunisation risks. By understanding the immune mechanisms involved, this research advocates for improved transfusion practices and further investigation into immune modulation to enhance transfusion safety, particularly for chronically transfused patients.

The study by Castro O et al., examines the risk of alloimmunisation in patients with SCD undergoing chronic transfusion therapy

[13]. The authors highlight that repeated transfusions increase exposure to non-self RBC antigens, leading to the development of alloantibodies, which complicate future transfusions. They discuss patient-specific factors, such as genetic background, antigenic differences between donor and recipient populations, and immune response variability as key determinants of alloimmunisation risk. The study underscores the importance of extended RBC antigen matching to reduce alloimmunisation rates in transfusion-dependent SCD patients.

The study by Pahuja S et al., focus on dual red cell alloimmunisation involving anti c and anti E antibodies, emphasising the challenges and management strategies in resource-limited settings [14]. The authors discuss how alloimmunisation complicates transfusion therapy, particularly in patients requiring chronic transfusions, by reducing the availability of compatible blood and increasing the risk of haemolytic transfusion reactions. They propose a systematic approach to the immunohematological work-up, highlighting the importance of early detection, extended antigen matching, and meticulous transfusion planning to minimise adverse outcomes. The study underscores the need for pragmatic and cost-effective strategies in settings with limited access to advanced immunohematology services. By advocating for improved transfusion protocols and laboratory support, the authors aim to enhance patient safety and optimise blood resource utilisation in low-resource environments.

The study by Mangwana S et al., highlight that repeated blood transfusions expose patients to foreign RBC antigens, increasing the likelihood of alloimmunisation, which can complicate future transfusions and lead to transfusion delays or haemolytic reactions [15]. They discuss factors influencing alloimmunisation risk, including the patient's immune response, antigenic disparities between donor and recipient populations, and the frequency of transfusions. The study underscores the importance of preventive strategies, such as extended RBC antigen matching, routine antibody screening, and the use of leukoreduced and phenotypically matched blood products, to minimise complications. By addressing these challenges, the authors advocate for improved transfusion practices to enhance the safety and efficacy of blood transfusion therapy in oncology patients.

CONCLUSION(S)

Red cell alloimmunisation presents a major challenge in managing patients who require chronic transfusions, especially those with conditions like SCD and beta thalassaemia major. The presence of alloantibodies complicates the transfusion process by making it harder to find compatible blood units and increasing the likelihood of transfusion reactions. To tackle these issues, various strategies have been proposed and implemented. These strategies include extended phenotyping and genotyping for antigens such as Rh, Kell, and Duffy, as well as providing antigen-matched blood for high-risk patients. Additionally, advancements in molecular techniques have enhanced the ability to conduct detailed genotyping, which is useful for identifying rare antigen profiles and ensuring better blood matching. Widespread implementation of these practices could significantly decrease the rates of alloimmunisation and improve clinical outcomes for patients in need of chronic transfusions.

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