Anti-c Alloimmunization Associated with Acute Hemolytic Transfusion Reaction in a Chronically Transfused β-Thalassemia Patient: A Case Report

Udaya Prakash Bhandari[1], MSc; Sabindra Maharjan[2], MSc; Sunil Bhasima[2], BSc; Bipin Nepal[1,2], MS

[1]T.U. Lions Blood Transfusion and Research Centre (TULBTRC), Kirtipur, Nepal
[2]Department of Transfusion Medicine, Grande International Hospital (GIH), Kathmandu, Nepal

ABSTRACT

Red blood cell (RBC) alloimmunization is a significant complication in chronically transfused patients with transfusion-dependent β-thalassemia. Antibodies directed against Rh antigens, particularly anti-c, are clinically important because they may lead to acute or delayed hemolytic transfusion reactions and complicate future transfusion support. We report the case of a 28-year-old woman with transfusion-dependent β-thalassemia who presented with severe anemia and acute febrile illness. Shortly after transfusion, she developed clinical features suggestive of acute hemolytic transfusion reaction accompanied by septic shock and coagulopathy. Immunohematological investigation revealed the presence of clinically significant anti-c alloantibody. Antibody screening and identification were performed using solid-phase red cell adherence technology on the Neo-Iris platform. Extended Rh phenotyping demonstrated compatibility with c-antigen–negative donor units (CCee) and incompatibility with a c-antigen–positive unit (CcEe), confirming anti-c specificity. The patient was subsequently transfused with two compatible c-negative packed red blood cell units, resulting in hematologic and clinical improvement without further transfusion-related complications. This case highlights the importance of routine antibody screening, extended Rh phenotyping, and provision of antigen-matched blood in chronically transfused patients to minimize alloimmunization and improve transfusion safety.

Keywords: β-thalassemia, alloimmunization, anti-c alloantibody, hemolytic transfusion reaction, Rh blood group system, extended phenotyping, antigen-matched transfusion

Introduction:

β-thalassemia is an inherited hemoglobin disorder characterized by reduced or absent β-globin chain synthesis, resulting in ineffective erythropoiesis and chronic anemia. Patients with transfusion-dependent β-thalassemia require lifelong RBC (red blood cells) transfusions for survival and improved quality of life. However, repeated transfusions expose patients to non-self RBC antigens, predisposing them to alloimmunization.[1]

RBC alloimmunization remains one of the most clinically significant non-infectious complications of chronic transfusion therapy. Alloantibodies most frequently target antigens within the Rh (C, c, E, e) and Kell systems.[2] Among these, anti-c is particularly important due to its ability to cause hemolytic transfusion reactions and its high immunogenicity compared to other minor Rh antigens.[3] We describe a case of acute hemolytic transfusion reaction due to anti-c alloimmunization in a chronically transfused β-thalassemia patient and discuss its clinical implications.

Case Report:

A 28-year-old female with transfusion-dependent β-thalassemia presented with acute febrile illness, generalized weakness, and progressive pallor. The patient had a long history of intermittent packed red blood cell transfusions over a decade. Her blood group was A Rh (D) positive. On admission, she was markedly pale and tachycardic. Initial laboratory findings revealed anemia with a hemoglobin level 4 g/dL along with bicytopenia and evidence of coagulopathy. Given the severity of anemia,

Correspondence:
Bipin Nepal, MS
Email: bipinnepal@hotmail.com
Received: 1/June/2026
Accepted: 28/June/2026
DOI: https://doi.org/10.3126/gmj.v6i1.100372

transfusion was initiated. Shortly after transfusion, the patient developed fever and hemodynamic instability consistent with septic shock. Clinical and laboratory findings raised suspicion for an acute hemolytic transfusion reaction.

Immunohematological Workup:

In view of suspected immune-mediated hemolysis, a detailed immunohematological evaluation was performed:

1. Blood group:

Forward and reverse ABO blood grouping, along with Rh (D) typing, were performed using standard immunohematological methods and confirmed the patient's blood group as A Rh (D) positive.

2. Antibody screening:

Antibody screening was performed using the Neo-Iris automated immunohematology analyzer manufactured by Werfen, employing solid-phase red cell adherence (SPRCA) technology.[4] The screening demonstrated positive reactivity shown in figure 1, prompting further immunohematological evaluation for identification of clinically significant alloantibodies.

3. Antibody identification:

Antibody identification was performed using an extended 14 red cell panel by solid-phase red cell adherence (SPRCA) technology. The antigram shown in figure 2 demonstrated a reaction pattern consistent with anti-c alloantibody. Panel cells lacking the c antigen (cells 1, 2 and 14) were non-reactive, whereas c-antigen–positive cells showed variable positive reactions ranging from 2+ to 3+. The autocontrol was negative, supporting the presence of an alloantibody rather than an autoantibody. The serologic findings were consistent with clinically significant anti-c alloimmunization within the Rh blood group system.

Management:

Following identification of anti-c alloantibody during antibody identification testing, an extended immunohematological compatibility assessment was undertaken to ensure safe transfusion support. Rh phenotyping of available donor red cell units was performed to identify c-antigen–negative compatible units.

Three donor units were phenotyped on Neo-Iris automated platform. As shown in table 1, two donor units demonstrated the Rh phenotype CCee, indicating absence of the c antigen, whereas one donor unit exhibited the phenotype CcEe and was therefore c-antigen positive.

Table 1 Donor Unit Phenotyping

Donor Unit	Rh Phenotype	Interpretation
1	CCee	c-antigen negative
2	CCee	c-antigen negative
3	CcEe	c-antigen positive

Indirect antiglobulin crossmatch testing was performed using column agglutination technology (CAT) gel cards from Ortho Clinical Diagnostics. The crossmatch demonstrated complete compatibility with both CCee donor units, while the CcEe donor unit demonstrated incompatibility at the antiglobulin phase shown in figure 3. The serological correlation between compatibility

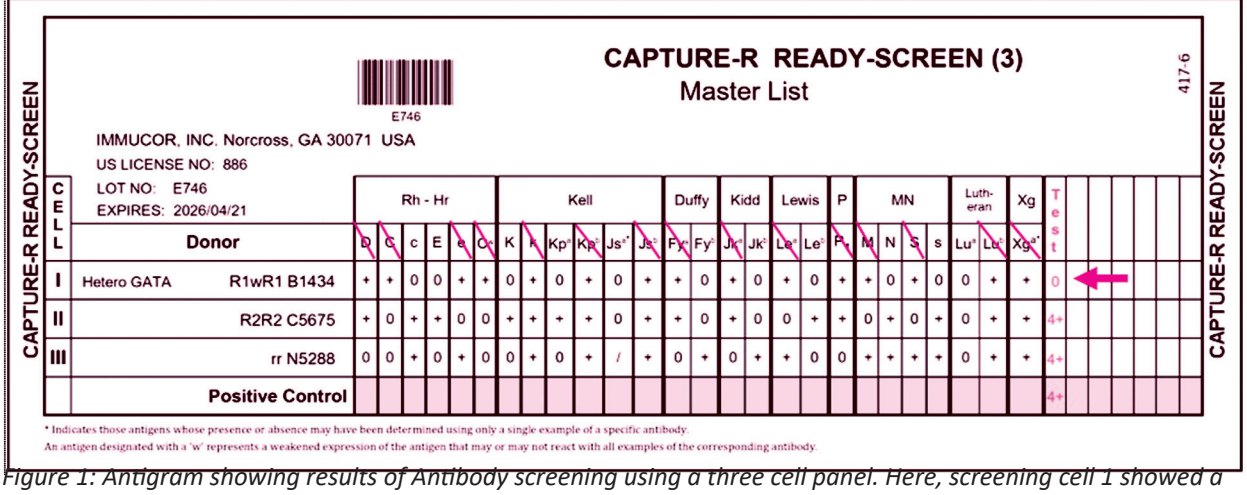

Figure 1: Antigram showing results of Antibody screening using a three cell panel. Here, screening cell 1 showed a negative reaction, whereas screening cell 2 and cell 3 demonstrated positive reactions indicating the likelihood of an antibody directed against a red cell antigen present on cells 2 and 3 but absent on cell 1. The reaction pattern was subsequently evaluated further by antibody identification studies.

CAPTURE-R READY-ID
Master List

ID506

NAME _____
NO. _____
INSTITUTION _____
BLOOD GROUP _____
ANTIBODY IDENTITY _____
TECH _____ DATE _____

IMMUCOR, INC. Norcross, GA 30071 USA
US LICENSE NO: 886
LOT NO: ID506
EXPIRES: 2026/03/20

CELL	Special Type	Donor	Rh - Hr						Kell						Duffy		Kidd		Lewis			P	MN				Luth-eran		Xg	CELL	PATIENT'S TEST RESULTS
			D	C	c	E	e	C^w	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	Le^a	P1	M	N	S	s	Lu^a	Lu^b	Xg^a		
1		RzR1 A3355	+	+	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	0	0	0	+	+	+	0	+	+	1	0
2		R1wR1 B11264	+	+	0	0	+	+	+	+	0	+	0	+	0	+	+	+	+	0	+	+	+	+	+	0	0	+	+	2	0
3		R2R2 C5811	+	0	+	+	0	0	0	+	0	+	0	+	+	+	0	+	+	0	+	+	+	0	+	+	0	+	0	3	3+
4		Ror D2991	+	0	+	0	+	0	0	+	0	+	/	+	0	0	0	+	0	0	+	+	+	0	0	+	0	+	0	4	2+
5		r'r E1254	0	+	+	0	+	0	0	+	0	+	/	+	0	+	+	+	0	+	+	+	+	+	+	+	0	+	+	5	2+
6		r"r F919	0	0	+	+	+	0	0	+	0	+	0	+	+	+	0	+	0	+	0	0	+	0	+	+	0	+	+	6	3+
7		rr H1771	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	+	0	+	+	+	+	0	+	0	0	+	+	7	2+
8		rr G2125	0	0	+	0	+	0	+	+	0	+	/	+	0	+	+	+	0	+	+	+	+	0	+	0	0	+	+	8	3+
9	Bg(a+)	rr H177	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	+	+	0	0	+	0	0	+	+	+	+	0	9	3+
10		rr H1984	0	0	+	0	+	0	0	+	+	+	0	+	+	0	+	0	+	0	+	0	+	0	+	0	+	+	0	10	3+
11		rr N5054	0	0	+	0	+	0	0	+	+	+	0	+	0	+	+	0	0	+	+	+	0	0	+	0	+	+	0	11	2+
12		rr H2226	0	0	+	0	+	0	0	+	0	+	/	+	+	0	0	+	0	+	+	+	+	0	+	0	+	+	+	12	3+
13		rr G1283	0	0	+	0	+	0	+	+	0	+	0	+	+	0	0	+	0	0	+	+	0	+	+	0	+	+	13	3+
14	Mi(a+), GP.Mur	R1R1 B9268	+	+	0	0	+	0	0	+	0	+	0	+	+	0	+	0	0	+	0	+	+	+	0	+	0	+	+	14	0
15		POSITIVE CONTROL	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	PC	4+
16		NEGATIVE CONTROL	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	NC	0

* Indicates those antigens whose presence or absence may have been determined using only a single example of a specific antibody.

NOTES:
An antigen designated with a 'w' represents a weakened expression of the antigen that may or may not react with all examples of the corresponding antibody.

426-20

PATIENT'S SERUM / ANTIBODY SCREEN LOT: I, II, III, IV

Figure 2: Antibody identification 14 cell panel. Antibody identification was performed using an extended red cell panel employing solid-phase red cell adherence (SPRCA) technology. The reaction pattern was consistent with the presence of anti-c alloantibody.

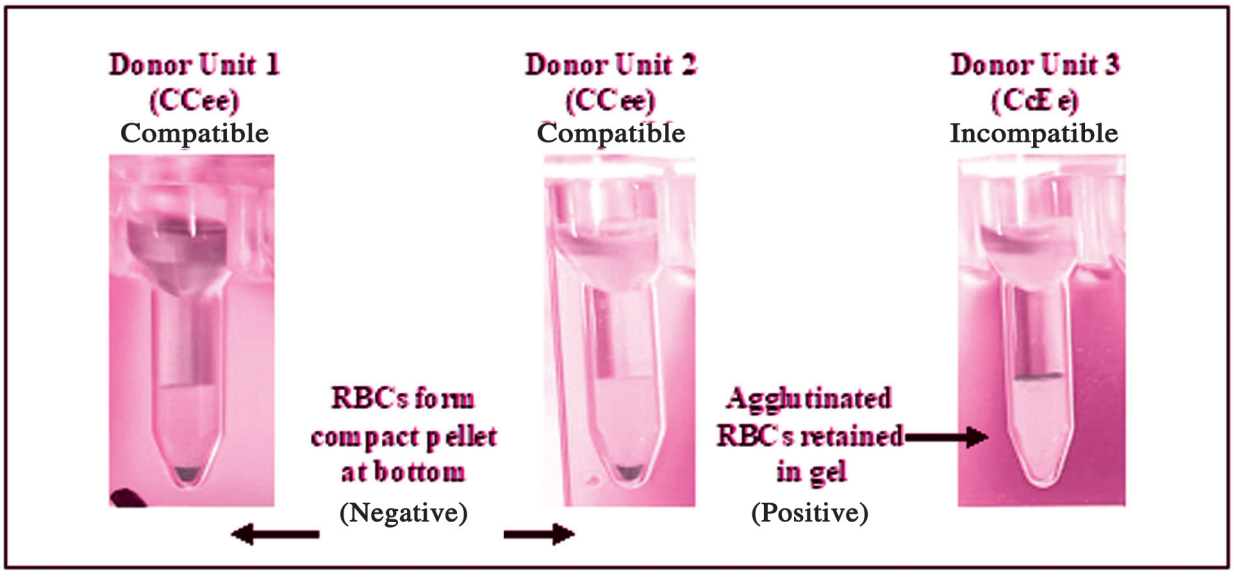

Figure 3: Crossmatch results by column agglutination technique (CAT) in the antiglobulin phase. Two c-negative donor units (Donor units 1 and 2; phenotype CCee) demonstrated a compatible reaction with a compact red cell pellet at the bottom of the gel column, whereas the donor unit expressing the c antigen (Donor unit 3; phenotype CcEe) showed incompatible reaction with agglutinated red cells retained within the gel column. These findings supported the presence of clinically significant anti-c alloantibody in the patient.

with c-negative units and incompatibility with the c-positive unit confirmed the clinical significance of the identified anti-c alloantibody. Based on these findings, transfusion of c-antigen–positive blood was avoided, and only c-antigen–negative packed red blood cell units were selected for transfusion. Two crossmatch-compatible CCee units were subsequently transfused under close clinical supervision with continuous monitoring for evidence of hemolysis or transfusion-related adverse reactions.

Outcome:

Following transfusion of c-antigen-negative compatible units, the patient's hemoglobin level increased to 8 g/dL and no further clinical or laboratory evidence of hemolysis was observed. The patient gradually recovered from septic shock and was discharged in hemodynamically stable condition.

Discussion:

Red cell alloimmunization remains one of the most important noninfectious complications in chronically transfused patients with transfusion-dependent β-thalassemia. Continuous exposure to foreign erythrocyte antigens during repeated transfusion therapy predisposes these patients to alloantibody formation, particularly against antigens within the Rh and Kell blood group systems. The reported prevalence of alloimmunization in β-thalassemia varies considerably across different populations, ranging from approximately 5% to more than 30%, depending on donor–recipient antigenic differences and local transfusion practices.[5,6] Among clinically significant alloantibodies, antibodies directed against Rh antigens are particularly important because of their strong immunogenicity and their association with hemolytic transfusion reactions. Anti-c is typically an IgG alloantibody reactive at 37°C and in the antiglobulin phase, capable of causing both acute and delayed hemolytic transfusion reactions.[6] Clinically, affected patients may present with fever, worsening anemia, jaundice, hemoglobinuria, and laboratory evidence of hemolysis; severe cases may progress to hemodynamic instability, disseminated intravascular coagulation, or multiorgan dysfunction.

In the present case, the patient developed transfusion-associated clinical deterioration in the setting of profound anemia and systemic inflammatory illness. Immunohematological evaluation demonstrated a clinically significant anti-c alloantibody, and the serological findings showed a clear correlation between antigen status and compatibility testing. Donor units with the CCee phenotype were compatible, whereas the CcEe donor unit demonstrated incompatibility at the antiglobulin phase. This pattern strongly supported anti-c as the causative alloantibody and highlights the importance of detailed antibody investigation in patients with suspected hemolytic transfusion reactions.[6] Several mechanisms may contribute to alloimmunization in chronically transfused thalassemia patients. Repeated antigenic exposure over time increases the likelihood of immune sensitization, particularly when donor red cell antigen profiles differ from those of recipients within highly immunogenic blood group systems such as Rh and Kell.[7,8]

This case also emphasizes the limitations of routine ABO and Rh(D) matching in multitransfused patients. Although standard compatibility testing reduces the risk of major hemolytic reactions, it does not prevent sensitization to other clinically significant Rh antigens such as C, c, E, and e.[9,10] Numerous studies have demonstrated that extended phenotypic matching for Rh and Kell antigens significantly reduces alloimmunization rates in transfusion-dependent populations.[8,10] From a transfusion medicine perspective, extended red cell phenotyping should ideally be performed before initiation of long-term transfusion therapy, particularly in patients with β-thalassemia and other chronic transfusion-dependent disorders. Once alloantibodies develop, transfusion support becomes increasingly complex due to difficulty in locating antigen-negative compatible units and the risk of additional alloantibody formation.[11]

The present case underscores the urgent need for implementation of routine antibody screening, extended Rh and Kell phenotyping, and establishment of antigen-typed donor registries in developing countries. Such strategies are essential to improve transfusion safety, minimize alloimmunization, and optimize long-term transfusion management in chronically transfused patients.

Conclusion:

This case highlights the potentially life-threatening consequences of red cell alloimmunization

in chronically transfused patients with β-thalassemia. The identification of clinically significant anti-c alloantibody was crucial in explaining the incompatible crossmatch findings and transfusion-associated hemolytic reaction. Successful management was achieved through timely immunohematological evaluation and transfusion of c-antigen–negative compatible red cell units. The case underscores the importance of routine antibody screening, extended Rh and Kell phenotyping, and antigen-matched transfusion strategies in patients requiring long-term transfusion support. Implementation of these practices may substantially reduce alloimmunization-related morbidity and improve transfusion safety, particularly in resource-limited settings.

References

1. Cappellini MD, Farmakis D, Porter J, Taher A, editors. 2021 Guidelines: For the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 4th ed. Nicosia (Cyprus): Thalassaemia International Federation; 2023.
2. Chaudhari CN. Red cell alloantibodies in multiple transfused thalassaemia patients. Medical Journal Armed Forces India. 2011 Jan 1;67(1):34-7. https://doi.org/10.1016/S0377-1237(11)80008-0
3. Daniels, G. (2013). Index. In Human Blood Groups, G. Daniels (Ed.). https://doi.org/10.1002/9781118493595.index
4. Jang MA, Oh JW, Lee ST, Seo JY, Kim DW. Evaluation of the Automated Blood Bank Systems Galileo NEO and QWALYS-3 for ABO-RhD Typing and Antibody Screening. Korean J Blood Transfus. 2014;25(3):235-242. DOI: http://doi.org/10.0000/kjbt.2014.25.3.235
5. Niazkar HR, Ghorbani M, Maleki MS, Jahangir H, Homapour F, Abbasnezhad A. Acute Hemolytic Transfusion Reaction Due to Anti-c Rhesus Antibody in a Patient With Subdural Hematoma: A Case Report Emphasizing the Shortcoming of Spin Cross-Match. Acta Medica Iranica. 2020 Jun 16:43-6.
6. Sachan D, Jayakumar R, Varghese J, Rela M. An acute hemolytic transfusion reaction due to the "anti-c" rhesus antibody: A case report emphasizing the role of transfusion medicine. Asian J Transfus Sci. 2015 Jul-Dec;9(2):213-5. https://doi.org/10.4103/0973-6247.154256
7. Singer ST, Wu V, Mignacca R, Kuypers FA, Morel P, Vichinsky EP. Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly asian descent. Blood. 2000 Nov 15;96(10):3369-73.
8. Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. N Engl J Med. 2021 Feb 25;384(8):727-743. https://doi.org/10.1056/NEJMra2021838
9. Joarder N, Afrida N, Rahman M, Harun M, Sultana W, Hossain S, Reza N. Prevalence of red cell alloantibodies in transfusion-dependent thalassemia: a cross-sectional study from Bangladesh. International Journal of Research in Medical Sciences. 2026 Mar;14(3):1. https://doi.org/10.18203/2320-6012.ijrms20260601
10. Vichinsky E, Neumayr L, Trimble S, Giardina PJ, Cohen AR, Coates T, Boudreaux J, Neufeld EJ, Kenney K, Grant A, Thompson AA; CDC Thalassemia Investigators. Transfusion complications in thalassemia patients: a report from the Centers for Disease Control and Prevention (CME). Transfusion. 2014 Apr;54(4):972-81; quiz 971. doi: 10.1111/trf.12348. Epub 2013 Jul 25. PMID: 23889533; PMCID: PMC4410835.
11. Westhoff CM. The Rh blood group system in review: a new face for the next decade. Transfusion. 2004 Nov;44(11):1663-73. https://doi.org/10.1111/j.0041-1132.2004.04237.x