

Access this article online
Quick Response Code:

Website: www.ajts.org
DOI: 10.4103/ajts.AJTS_137_17

# Red blood cell alloimmunization in Iran: A Comprehensive review of the literature

Maryam Sadat Hosseini, Leila Jafari, Reza Shiri Heris, Ahmad Gharehbaghian

## Abstract:

**BACKGROUND:** Alloimmunization is an immune response against foreign antigens which introduced into the body through transfusion, pregnancy, or transplantation. This phenomenon is a big challenge in patients, which require regular transfusions. In the current study, we tried to have a comprehensive review on the status of alloimmunization in Iran. For this purpose, we searched for papers investigating alloimmunization in transfusion-dependent patients and also in patients with no regular transfusions who are candidate for surgery or who need blood.

**METHODS:** We searched PubMed, Google Scholar, SID, and MAGIRAN databases using the following keywords: “blood transfusion,” “alloimmunization,” “alloantibodies,” “irregular antibodies,” “red cell antibodies,” and “Iran.” No limitation for the date of publication and language of the papers was defined. All the identified records were then screened for the relevance and duplication.

**RESULTS:** A total of 22 papers were included in this study. All of the studies were conducted from 1999 to 2016 and providing alloimmunization data from different cities all over of Iran. In general, the results showed that the most prevalent alloantibodies are anti-Kell (anti-K antigen) and anti-Rh system, mainly anti-E, anti-D, anti-C, and anti-c.

**CONCLUSION:** Anti-Kell and anti-Rh antibodies are the most prevalent antibodies responsible for alloimmunization in Iranian population.

## Keywords:

Alloantibody, alloimmunization, Iran, transfusion

## Introduction

Since the first published report on human-to-human blood transfusion by James Blundell,<sup>[1]</sup> blood transfusion has become a relatively simple and life-saving part of daily medical practice. Allogeneic blood transfusion is a form of temporary transplantation. This procedure introduces a multitude of foreign antigens into the recipient, and thereby can stimulate the immune system. The incidence of transfusion-induced alloimmunization is debated and ranges from 1% to 3% in single-transfused individuals to 30% in

multitransfused patients (e.g., sickle cell disease, thalassemia, and myelodysplasia).<sup>[2]</sup> The most commonly involved antigens are classified in the following categories: (1) red blood cell (RBC)-specific antigens; (2) granulocyte-specific antigens; (3) platelet-specific antigens (human platelet antigens); and human leukocyte antigens.<sup>[3,4]</sup>

With the improvement of health-care systems and medical technologies, there has been an increase in the number of chronic patients and also in major surgeries which require a higher number of blood transfusions. Thus, the frequency of RBC alloantibodies is increasing. The development of blood cell antibodies (alloantibodies and/or autoantibodies)

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Hosseini MS, Jafari L, Shiri Heris R, Gharehbaghian A. Red blood cell alloimmunization in Iran: A comprehensive review of the literature. *Asian J Transfus Sci* 2020;14:4-8.

Department of Laboratory  
Hematology and Blood  
Banking, School of Allied  
Medical Sciences, Shahid  
Beheshti University of  
Medical Sciences, Tehran,  
Iran

## Address for correspondence:

Dr. Ahmad  
Gharehbaghian,  
Department of Laboratory  
Hematology and Blood  
Banking, School of  
Allied Medical Sciences,  
Shahid Beheshti  
University of Medical  
Sciences, Tehran, Iran.  
E-mail: gharehbaghian@  
sbmu.ac.ir

Submission: 06-11-2017  
Accepted: 07-01-2018  
Published: 24-07-2020

remains a significant challenge in transfusion therapy which limits the provision of compatible blood products for future transfusions. In the current study, we tried to have a comprehensive review on the status of red cell alloimmunization in Iranian population.

## Methods

### Search strategy

For this review study, we tried to collect all the related studies on alloimmunization against RBCs in Iranian patient population who underwent elective surgery or multitransfused patients. We searched PubMed, Google Scholar, SID, and MAGIRAN databases using the following keywords: "blood transfusion," "alloimmunization," "alloantibodies," "irregular antibodies," "red cell antibodies" and "Iran." No limitation for the date of publication was defined and studies in either Persian or English languages were included.

All the identified records were then screened for the relevance of title and content. In the next step, duplicate papers which seem to have an overlap in their studied subjects were excluded. Figure 1 illustrates a schematic view of the search strategy.

### Data extraction

We extracted the year of publication, number of included subjects, region of the study, proportion of patients with alloantibody/autoantibody, and type of the most commonly detected alloantibodies with their related frequencies.

## Results

### Search results

In the initial search, we identified a total of 31 papers. All 31 papers were assessed through abstracts and 7 papers

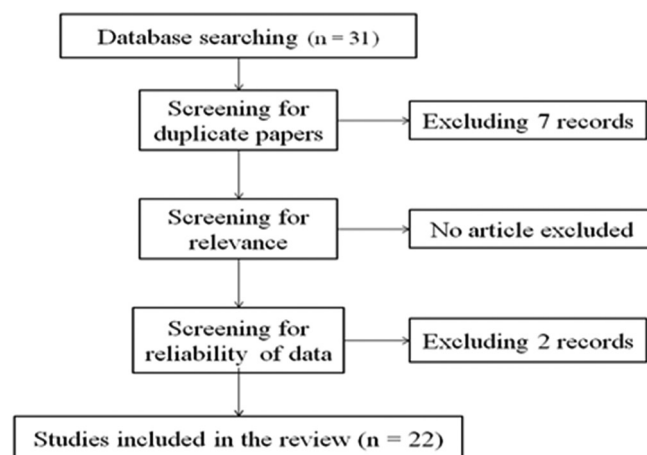


Figure 1: Summary of the search strategy

were removed because of duplication or because they seem to have an overlap in the studied subjects. We also removed two papers because of the incomplete data. Finally, a total of 22 papers were included in this study, of which 10 papers were in Persian and 12 in English.

### Extracted data

All of the studies were conducted from 1999 to 2016 and providing alloimmunization data from different cities/provinces all over of Iran. Most of the studies were conducted on patients with transfusion-dependent  $\beta$ -thalassemia (either with intermediate or major disease). The data of these studies are summarized in Table 1. In three out of 22 papers, patients without regular transfusions who were candidate for surgery or need blood underwent the assessment for antibody screening. Table 2 demonstrates an overview of these three studies.

## Discussion

In most blood transfusion services, phenotyping and pretransfusion compatibilization of the most immunogenic antigens are normally applied to patients with chronic diseases.<sup>[26]</sup> However, the risk of alloantibody development still remains a big challenge, particularly in developing countries where high costs of pretransfusion phenotyping do not allow it to be a part of routine transfusion procedure.

Alloimmunization is more highlighted in cases with regular transfusions, including patients with chronic anemia such as  $\beta$ -thalassemia major (or intermediate) and sickle cell disease, patients who underwent bone marrow transplantation, patients under heavy chemotherapeutic regimens, and lots of other conditions.<sup>[2,27]</sup>

The blood transfusion services aim to provide a high-quality facility with no to minimum risk to the recipients. When humans are involved in any critical steps in the process of transfusion, errors are inevitable. Crossmatch is a critical step in pretransfusion testing which may be affected by a wide range of clerical and technical errors, such as mislabeled or partially labeled tubes, misinterpretation of hemolysis in serum grouping as negative, and blood group discrepancy due to inadequate washing of cells.<sup>[28]</sup> A prospective study was performed at a blood center (18-month duration) to determine errors reported in the crossmatch laboratory. This study shows the importance of blood sample collection process and pretransfusion testing in preventing errors during transfusion.<sup>[28]</sup>

Furthermore, alloimmunization can occur because many alloantibodies may not be detected, as no further transfusions are required or because the titer of antibodies decrease over time and reaches a nondetectable level

**Table 1: Studies which assessed red cell immunization among Iranian patients with transfusion-dependent  $\beta$ -thalassemia**

Authors (references)	Year of publication	Number of patients	Region of study*	Incidence of immunization, n (%)	Prevalence of alloantibodies (%)
Davari and Soltanpour <sup>[5]</sup>	2016	49	Zanjan	16.32 (allo-Ab)	Anti-K (60) Anti-E (10) Anti-c (10) Anti-Leb (10)
Younesi et al. <sup>[6]</sup>	2016	240	Tehran	37.1	Anti-K (46.7) Anti-E (18.1) Anti-D (11.4) Anti-C (6) Anti-c (4) Anti-Cw (3) Anti-Fyb (3) Anti-Lua (3) Anti-s (2) Anti-e (1)
<sup>#</sup> Vaziri et al. <sup>[7]</sup>	2015	100	Yazd	4 (allo-Ab)	Anti K (75) Anti-C, Anti-D (25)
Keikhaei et al. <sup>[8]</sup>	2013	133	Ahvaz	18.7 (allo-Ab) 12.7 (auto-Ab)	Rh subgroups system (55) Kell system (33) Undetermined (3.1)
Mirzaeian et al. <sup>[9]</sup>	2013	385	Zahedan	17.9 (allo-Ab) 5.5 (auto-Ab)	Anti-E (2.6) Anti-C (1.6) Anti-Lua (1.6) Anti-c (1.3) Anti-Cw (1.3) Anti-K (1)
Tahannejad-Asadi et al. <sup>[10]</sup>	2013	70	Ahvaz	55 (allo-Ab)	Anti-K (4.3) Anti-E (2.2) Anti-D (2.2)
Kosaryan et al. <sup>[11]</sup>	2012	218	Sari	40.4 (allo-Ab)	Anti- C, Cw, Lea (40)
Azarkeivan et al. <sup>[12]</sup>	2011	835	Multicenter (Tehran, Ghazvin, Karaj)	12.1 (allo-Ab) 1 (auto-Ab)	Anti-Kell (33.7) Anti-D (10.9) Anti-E (9.9)
Obeidi et al. <sup>[13]</sup>	2011	90	Bushehr	10 (allo-Ab)	Anti-K (18)
Ansari et al. <sup>[14]</sup>	2009	458	Tehran (Ali asghar hospital)	11.8 (allo)	Anti-Kell or Anti-Rh (81.6) Other (18.3)
Sadeghian et al. <sup>[15]</sup>	2009	313	Mash' had	2.87 (allo-Ab)	Anti-D (88.8) Anti-C (33.3) Anti-E (11.1)
Shamsian et al. <sup>[16]</sup>	2008	121	Tehran (Mofid children's hospital)	7.4 (allo-Ab)	Anti-K (1.6) Anti-D (1.6)
Karimi et al. <sup>[17]</sup>	2007	711	Shiraz	5.34 (allo-Ab)	Anti-K (19) Anti-D (6) Anti-E (4)
Kiani et al. <sup>[18]</sup>	2006	65	Lorestan	1.53	Anti-E (100)***
Eshghi <sup>[19]</sup>	2003	163	Zahedan	0	-
Rahgozar et al. <sup>[20]</sup>	2003	52	Isfahan	76.9	Anti-K (27.5) Anti-N (12.5) Anti-Cw (5) Anti-s (5) Anti-Fyb (5)

Contd...

**Table 1: Contd...**

Authors (references)	Year of publication	Number of patients	Region of study*	Incidence of immunization, n (%)	Prevalence of alloantibodies (%)
Farsinejad and Poorfathollah <sup>21</sup>	2003	300	Kerman	9 (allo-Ab)	Anti-Rh (47.7) Anti-MNS (9.1) Anti- kidd (6.8)
Ahmadji <sup>22</sup>	2001	142	Kermanshah	9.2	Anti-LUa (61.5) Anti-P1 (24.1) Anti-C (7.7) Anti-N (7.7)
Kaviani et al.	1999	100	Tehran and West Azerbaijan	10	Not mentioned**

\*Patients studied in each region may be native or not, #This study also included 24 Afghan patients, \*\*The authors introduced Anti-Rh and Anti-Kell systems as the most common antibodies, but the exact incidence was not mentioned, \*\*\*Only one patient (1.53) was detected to have alloantibody which was against E antigen. Ab = Antibody

**Table 2: Studies which assessed red cell alloimmunization among Iranian patients without regular transfusions**

Authors (references)	Year of publication	Subjects	Number of patients	Region of study*	Incidence of alloimmunization, n (%)	Prevalence of alloantibodies (%)
Gharehbaghian et al. <sup>23</sup>	2014	-	1420	Ardebil	0.92	Anti-K (30) Anti-E (15) Anti-c (15)
Khademi et al. <sup>24</sup>	2013	-	3092	Tehran	0.9	Anti-K (23.53) Anti-E (20.59) Anti-c (17.56)
Ghorbani Ali-Abadi et al. <sup>25</sup>	2013	-	3487	Shiraz	0.8	Anti-K (23) Anti-E (15) Anti-C (11)

\*Patients studied in each region may be native or not

before testing.<sup>26</sup> This phenomenon may also result from inappropriate methods of antibody detection. Anyway, it is an inevitable outcome of transfusion since the compatibility of all the transfused antigens is impossible.

Most of the studies on alloimmunization in Iranian patients included subjects with  $\beta$ -thalassemia (either intermediate or major). According to these studies, most of the detected alloantibodies are anti-Kell (anti-K antigen) and anti-Rh system antibodies mainly anti-E, anti-D, anti-C, and anti-c [Table 1]. We also found three studies which conducted on patients without regular transfusions who were candidate for elective surgery. These studies included a higher number of patients and provided more general data of Iranian population. Based on these studies, the most common cause of alloimmunization in males is transfusion and in females is pregnancy. All three papers introduced anti-K, anti-E, and anti-C/anti-c as the most common detected antibodies [Table 2]. The results of these studies are in agreement with the data obtained from thalassemic patients.

The development of anti-D antibody as one of the most common alloantibodies shows that we have still problems in blood group typing because D antigen is one the main antigens which should be matched between donor and recipient, especially for young female recipients. This problem may reflect clerical and technical errors made

by the staff and also inappropriate or incomplete quality control of the reagents and equipment. Human errors may affect all the steps in a transfusion procedure; including prescription and request, patient sampling, pretransfusion testing, and finally the collection of the component from the blood refrigerator and administration to the patient.<sup>29</sup> According to the literature, such errors considered as the main cause of transfusion reactions.

Our study with gathering the majority of studies on Iranian population from all over the country may provide an overview on the status of alloimmunization in Iran including the total incidence and the prevalence of responsible antibodies. Our review may also provide a better view for the future studies which in turn may lead to better management of the problem.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

- Blundell J. Experiments on the transfusion of blood by the syringe. *Med Chir Trans* 1818;9:56-92.
- Thakral B, Saluja K, Sharma RR, Marwaha N. Red cell

- alloimmunization in a transfused patient population: A study from a tertiary care hospital in North India. *Hematology* 2008;13:313-8.
3. Gamit S, Shah P, Iyer R. Role of red blood cells (RBCs) alloimmunization in multiple transfusions. *Southeast Asian J Case Rep Rev* 2015;4:1137-52.
  4. Brouk H, Bertrand G, Zitouni S, Djenouni A, Martageix C, Griffi F, et al. HPA antibodies in Algerian multitransfused patients: Prevalence and involvement in platelet refractoriness. *Transfus Apher Sci* 2015;52:295-9.
  5. Davari K, Soltanpour MS. Study of alloimmunization and autoimmunization in Iranian  $\beta$ -thalassemia major patients. *Asian J Transfus Sci* 2016;10:88-92.
  6. Younesi MR, Louni Aligoudarzi S, Bigdeli R, Lashgari M, Mazaheri H, Asgary V, et al. Alloimmunization against platelets, granulocytes and erythrocytes in multi-transfused patients in Iranian population. *Transfus Apher Sci* 2016;55:205-11.
  7. Vaziri M, Javadzadeh Shahshahani H, Moghaddam M, Taghvaei N. Prevalence and specificities of red cell alloantibodies in transfusion-dependent beta thalassemia patients in Yazd. *Iran J Ped Hematol Oncol* 2015;5:93-9.
  8. Keikhaei B, Hirad Far A, Abolghasemi H, Mousakhani H, Ghanavat M, Moghadam M, et al. Red blood cell alloimmunization in patients with thalassemia major and intermediate in Southwest Iran. *Iran J Blood Cancer* 2013;6:41-6.
  9. Mirzaeian A, Tamaddon G, Naderi M, Hosseinpour M, Sargolzaie N, Dorgalaleh A. Prevalence of alloimmunization against RBC antigens in thalassemia major patients in South East of Iran. *J Blood Disord Transf* 2013;4:2.
  10. Tahannejad-Asadi Z, Elahi A, Mohseni A, Talebi M, Khosravi M, Jalalifar MA. Screening and identifying of erythrocyte alloantibodies in patients with thalassemia major referred to Ahvaz Shafa hospital. *Feyz J Kashan Univ Med Sci* 2013;17:165-72.
  11. Kosaryan M, Mahdavi MR, Roshan P, Hojjati MT. Prevalence of alloimmunisation in patients with beta thalassaemia major. *Blood Transfus* 2012;10:396-7.
  12. Azarkeivan A, Ansari S, Ahmadi MH, Hajibeigy B, Maghsudlu M, Nasizadeh S, et al. Blood transfusion and alloimmunization in patients with thalassemia: Multicenter study. *Pediatr Hematol Oncol* 2011;28:479-85.
  13. Obeidi N, Mankhian AR, Hatami G, Emami H. Antibody screening in patients with thalassemia major. *Lab Med* 2011;42:618-21.
  14. Ansari S, Azarkivan A, Salahmand M, Lotfi P. Assessment of alloimmunization in multi transfuse (Thalassemia) patients admitted in ali asghar children's hospital during 2004-05. *Razi J Med Sci* 2009;16:65-72.
  15. Sadeghian MH, Keramati MR, Badiei Z, Ravarian M, Ayatollahi H, Rafatpanah H, et al. Alloimmunization among transfusion-dependent thalassemia patients. *Asian J Transfus Sci* 2009;3:95-8.
  16. Shamsian BS, Arzani MT, Shamshiri AR, Alavi S, Khojasteh O. Frequency of red cell alloimmunization in patients with  $\beta$ -major thalassemia in an Iranian referral hospital, Iran. *J Pediatr* 2008;18:149-53.
  17. Karimi M, Nikrooz P, Kashef S, Jamalian N, Davatolhagh Z. RBC alloimmunization in blood transfusion-dependent beta-thalassemia patients in Southern Iran. *Int J Lab Hematol* 2007;29:321-6.
  18. Kiani A, Shirkhani Y, Kashi M, Abdi J. Prevalence of alloimmunization against RBC antigens in thalassemia major patients of Lorestan province in 1383. *The Scientific Journal Of Iranian Blood Transfusion Organization (Khoon)* 2006;3:265-71.
  19. Eshghi P. Evaluation of alloimmunization in major B. thalassaemic patients in Zahedan in 2001. *J Mazandaran Univ Med Sci* 2003;13:36-42.
  20. Rahgozar S, Moafi A, Yavari F, Hourfar H. Alloantibody detection in major beta thalassaemic patients transfused within less-than-20-day intervals. *The Scientific Journal Of Iranian Blood Transfusion Organization (Khoon)* 2005;1:1-9.
  21. Farsinejad A, Poorfathollah Aa. Evaluation of immune antibodies against red cells in thalassaemic patients in Kerman Province. *Modares J Med Sci* 2002;5:93-9.
  22. Ahmadi D. Frequency of minor blood group alloantibodies in beta-thalassemia major blood recipients in Kermanshah (1999). *Journal Of Kermanshah University Of Medical Sciences (Behbood)* 2001;5:50-5.
  23. Gharehbaghian A, Ghezelbash B, Aghazade S, Hojjati MT. Evaluation of alloimmunization rate and necessity of blood type and screening test among patients candidate for elective surgery. *Int J Hematol Oncol Stem Cell Res* 2014;8:1-4.
  24. Reyhaneh K, Ahmad G, Gharib K, Vida V, Raheleh K, Mehdi TN, et al. Frequency & specificity of RBC alloantibodies in patients due for surgery in Iran. *Indian J Med Res* 2013;138:252-6.
  25. Ghorbani Ali-Abadi E, Tavassoli A, Gharehbaghian A, Kasraian L, Khademi R, Taleie A. Evaluation of frequency and specificity of RBC alloantibodies in Namazi hospital patients in Shiraz, 2010. *Sci J Iran Blood Transfus Organ* 2013;10:239-45.
  26. Schonewille H, van de Watering LM, Brand A. Additional red blood cell alloantibodies after blood transfusions in a nonhematologic alloimmunized patient cohort: Is it time to take precautionary measures? *Transfusion* 2006;46:630-5.
  27. Santos FW, Magalhães SM, Mota RM, Pitombeira MH. Post-transfusion red cell alloimmunisation in patients with acute disorders and medical emergencies. *Rev Bras Hematol Hemoter* 2007;29:369-72.
  28. Tondon R, Pandey P, Mickey KB, Chaudhary R. Errors reported in cross match laboratory: A prospective data analysis. *Transfus Apher Sci* 2010;43:309-14.
  29. Stainsby D, Russell J, Cohen H, Lilleyman J. Reducing adverse events in blood transfusion. *Br J Haematol* 2005;131:8-12.