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Red Blood Cell Alloimmunization Among Chronically Transfused Patients: A Systematic Review of Prevalence, Risk Factors, and Clinical Outcomes

Lorreine Denise W. Castañares*, Franrey Rose S. Buscado, Anthony Vince P. Bongo, Kerstine Marie T. Yara-Castro, and Jemimah May B. Llanto

Department of Medical Technology, Cebu Doctors' University, Mandaue City, Philippines

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*Corresponding Author: **Lorreine Denise W. Castañares** | Email Address: **lorreinecastanares0321@gmail.com**

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Abstract

Background: *Red blood cell (RBC) alloimmunization is a significant complication of repeated blood transfusions, particularly among patients with sickle cell disease, thalassemia, and other hematological disorders requiring long-term transfusion support. The development of RBC alloantibodies can complicate compatibility testing, limit the availability of suitable blood, and increase the risk of transfusion-related complications.*

Objective: *This systematic review aimed to evaluate the prevalence, alloantibody specificities, associated risk factors, clinical outcomes, and preventive strategies related to RBC alloimmunization among chronically transfused patients.*

Methods: *A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Literature searches were performed across PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library. Of 327 identified records, 37 studies met the eligibility criteria and were included in the qualitative synthesis. Data concerning study characteristics, alloimmunization prevalence, antibody specificities, risk factors, clinical outcomes, and transfusion practices were extracted and synthesized narratively because of clinical and methodological heterogeneity.*

Results: *RBC alloimmunization prevalence varied considerably across patient populations and geographical settings. Among patients with thalassemia, reported prevalence ranged from 2.9% to 32.5%, while selected sickle cell disease cohorts reported frequencies ranging from 14.4% to 31.3%. Antibodies against the Rh and Kell blood group systems predominated, particularly anti-E, anti-K, anti-C, and anti-c. Cumulative transfusion exposure, older age at first transfusion, splenectomy, and immunological or genetic characteristics were identified as potential risk factors, although associations were inconsistent across studies. Alloimmunization was associated with increased complexity of transfusion compatibility management, while evidence concerning long-term clinical complications remained limited. Extended antigen matching demonstrated potential preventive benefits, although alloantibody formation persisted in some patients despite prophylactic matching.*

Conclusion: *RBC alloimmunization remains an important challenge in the management of chronically transfused patients. Variations in prevalence and associated risk factors highlight the multifactorial nature of alloantibody development. Regular antibody screening, extended antigen matching, comprehensive transfusion documentation, and individualized transfusion strategies may improve transfusion safety. Further high-quality prospective studies are needed to clarify risk factors, evaluate long-term clinical outcomes, and establish the effectiveness of preventive strategies.*

Keywords: *Red blood cell alloimmunization, chronic blood transfusion; alloantibodies; prevalence; risk factors; sickle cell disease; thalassemia; transfusion safety; systematic review.*

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1. Introduction

Red blood cell (RBC) alloimmunization is an immune-mediated process characterized by the production of antibodies against foreign erythrocyte antigens following exposure through blood transfusion or pregnancy. This response occurs when the recipient's immune system recognizes non-self RBC antigens and initiates an adaptive immune response, potentially resulting in clinically significant alloantibody formation [1]. RBC alloantibodies are commonly associated with the Rh, Kell, Kidd, Duffy, and MNS blood group systems, which differ in antigen immunogenicity, antibody persistence, and clinical significance [2, 3]. Alloimmunization is particularly important among chronically transfused patients because repeated exposure to donor erythrocyte antigens increases opportunities for immune sensitization, although individual susceptibility varies considerably [1, 4]. The development of these antibodies presents substantial challenges in transfusion medicine, including difficulties obtaining compatible blood, increased laboratory investigations, and potentially serious transfusion-related complications [5, 6].

The detection and management of RBC alloimmunization require appropriate immunohematological investigations, including antibody screening, antibody identification, indirect antiglobulin testing, and serological crossmatching. Additional techniques, such as direct antiglobulin testing, extended RBC phenotyping, and molecular blood group genotyping, may support antibody characterization and the selection of compatible blood components [7, 9, 10]. Molecular methods are particularly useful among chronically transfused patients because circulating donor erythrocytes may interfere with conventional serological phenotyping [7]. Furthermore, previously identified alloantibodies may decline below detectable levels, a phenomenon known as antibody evanescence, but can reappear following subsequent antigen exposure and contribute to delayed hemolytic transfusion reactions [11, 12]. Consequently, comprehensive transfusion histories, accurate antibody records, and regular pretransfusion compatibility testing are essential for minimizing alloimmunization-related complications and improving long-term transfusion safety [3, 6]. Chronic RBC transfusion therapy remains an essential component of treatment for several inherited and acquired disorders, particularly sickle cell disease, transfusion-dependent thalassemia, myelodysplastic syndromes, and selected cases of chronic kidney disease and bone marrow failure [14]. Although repeated transfusions improve oxygen delivery, correct severe anemia, and support survival, cumulative exposure to donor RBC antigens increases the likelihood of alloantibody development [15]. The reported prevalence of alloimmunization varies substantially across clinical populations and geographical settings, reflecting differences in underlying diagnoses, transfusion exposure, donor–recipient antigen compatibility, genetic background, antibody detection methods, and transfusion practices [16, 17].

Patients with sickle cell disease may be particularly susceptible because of differences in RBC antigen frequencies between donors and recipients, variations in the *RHD* and *RHCE* genes, and inconsistent availability of prophylactically antigen-matched blood [18, 19]. Nevertheless, alloimmunization also represents an important concern among patients with thalassemia and other conditions requiring repeated transfusions, emphasizing the need to examine its burden across multiple patient populations rather than individual diseases alone [20, 21]. The importance of alloimmunization in thalassemia has also been addressed by Zarrabian et al. [22], who reviewed red cell alloimmunization among transfusion-dependent and transfusion-independent patients with β-thalassemia in the Eastern Mediterranean Region.

The burden of RBC alloimmunization is further influenced by geographical differences in blood group antigen distributions, population genetics, disease prevalence, healthcare resources, and transfusion-service infrastructure [23, 24]. In sub-Saharan Africa, where sickle cell disease is highly prevalent, limited access to extended antigen matching, comprehensive antibody screening, and specialized immunohematological services may complicate transfusion management [25]. Similarly, the long-term transfusion requirements of patients with thalassemia create important challenges in the Mediterranean region, the Middle East, and South and Southeast Asia [26, 27]. Differences in donor–recipient antigen profiles, screening protocols, and the availability of extended phenotyping or molecular genotyping may contribute to the observed variation in alloimmunization frequencies across healthcare systems [8, 25]. The relevance of hemoglobin disorders to transfusion medicine is also reflected in investigations of hemoglobin genotype distribution among Filipino populations [28]. These regional and institutional variations highlight the importance of interpreting alloimmunization prevalence within specific clinical and demographic contexts rather than assuming uniform risk across populations.

Several demographic, clinical, immunological, and transfusion-related factors have been investigated as potential determinants of RBC alloimmunization. These include cumulative transfusion exposure, age at initiation of transfusion therapy, splenectomy, underlying disease, recipient immune responsiveness, and donor–recipient antigen disparities [4, 8, 20]. However, associations between these factors and alloantibody development have not been consistently demonstrated across studies. In addition, antibodies against the Rh and Kell blood group systems are frequently reported, suggesting that antigen matching beyond standard ABO and RhD compatibility may have an important preventive role [3, 7]. Although extended antigen matching and improved antibody-screening practices have been recommended, questions remain regarding their comparative effectiveness, feasibility, and implementation across different patient populations and healthcare settings [29, 30].

Despite advances in transfusion medicine, important evidence gaps remain concerning the prevalence, associated risk factors, and clinical consequences of RBC alloimmunization among chronically transfused patients. Existing investigations frequently focus on specific diseases, particularly sickle cell disease and thalassemia, while differences in study design, sample size, transfusion history, antibody detection methods, and definitions of chronic transfusion exposure limit direct comparisons [20, 21]. Furthermore, although many studies report alloimmunization frequencies and antibody specificities, fewer comprehensively examine associated clinical outcomes, including delayed hemolytic transfusion reactions, difficulties obtaining compatible blood, transfusion delays, and long-term complications [11]. Evidence evaluating the clinical benefits of preventive antigen-matching strategies also remains limited, particularly across diverse healthcare environments [7, 30]. These limitations establish the need for a systematic synthesis integrating epidemiological findings, antibody characteristics, risk factors, clinical outcomes, and preventive transfusion practices.

Therefore, this systematic review aims to evaluate the prevalence, risk factors, and clinical outcomes of RBC alloimmunization among chronically transfused patients across different clinical and geographical settings. Specifically, it seeks to determine the reported prevalence of alloimmunization among different patient populations; identify predominant alloantibody specificities and blood group systems; examine demographic, clinical, immunological, and transfusion-related risk factors; assess clinical consequences, including hemolytic transfusion reactions, transfusion delays, and difficulties obtaining compatible blood; and evaluate the implications of antigen-matching and antibody-screening strategies for transfusion safety. By synthesizing available evidence, this review seeks to clarify variations in alloimmunization burden, identify existing knowledge gaps, and provide an evidence-based foundation for improving transfusion management and guiding future research among patients requiring long-term RBC transfusion therapy.

2. Methodology

2.1. Study Design and Protocol Registration

This study employed a systematic review design to evaluate the prevalence, risk factors, and clinical outcomes of red blood cell (RBC) alloimmunization among chronically transfused patients. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting guidelines to promote transparency, methodological consistency, and reproducibility in study identification, selection, critical appraisal, and evidence synthesis [31].

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO). Registration Number: [CRD420261547946] [32].

2.2. Literature Search Strategy

A comprehensive literature search was conducted across five electronic databases: PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library. The search strategy incorporated the terms "red blood cell alloimmunization," "erythrocyte alloantibodies," "chronic transfusion," "multiple blood transfusions," "prevalence," "risk factors," and "clinical outcomes," combined using Boolean operators (AND and OR). Reference lists of relevant publications were also examined to identify additional eligible studies. The search covered publications from database inception to the final search date, without geographical restrictions.

2.3. Eligibility Criteria

Eligible studies comprised peer-reviewed observational investigations, including cross-sectional, case-control, and cohort studies involving patients who received repeated RBC transfusions for sickle cell disease, thalassemia, myelodysplastic syndromes, chronic kidney disease, and other conditions requiring long-term transfusion support. Studies were included if they reported at least one relevant outcome, such as alloimmunization prevalence, alloantibody specificities, associated risk factors, clinical complications, or preventive transfusion practices.

Case reports, narrative reviews, editorials, animal studies, conference abstracts without sufficient extractable data, and investigations involving exclusively non-chronically transfused populations were excluded. Studies involving mixed patient populations were considered eligible when relevant data for repeatedly or chronically transfused patients could be identified and extracted.

2.4. Study Selection

The literature search identified 327 records across the five electronic databases. Following the removal of 42 duplicates, 285 records underwent title and abstract screening, of which 206 were excluded based on the eligibility criteria. Subsequently, 79 reports were sought for full-text retrieval; five could not be retrieved, leaving 74 articles for full-text assessment. Following eligibility evaluation, 37 articles were excluded, and the remaining 37 studies were included in the final qualitative synthesis.

The included studies provided evidence on alloimmunization prevalence, antibody specificities, associated risk factors, clinical consequences, and preventive transfusion strategies across different patient populations and geographical settings. The study identification, screening, eligibility assessment, and inclusion process is presented in the PRISMA 2020 flow diagram (Figure 1).

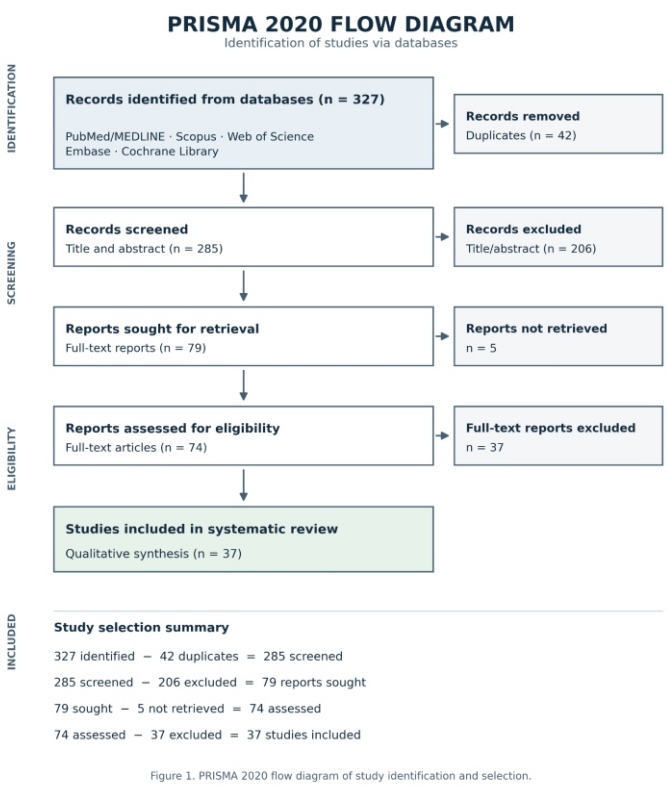


Figure 1. PRISMA 2020 flow diagram of study identification and selection.

2.5. Data Extraction

Data were extracted using a standardized extraction framework covering author names, publication year, geographical location, study design, sample size, participant characteristics, underlying clinical conditions, transfusion frequency, cumulative transfusion exposure, antibody screening methods, alloimmunization prevalence, and identified antibody specificities. Additional variables included demographic and clinical risk factors, antigen-matching practices, autoantibody formation, hemolytic transfusion reactions, difficulties obtaining compatible blood, and other reported clinical outcomes. Extracted information was reviewed for accuracy, consistency, and completeness before evidence synthesis.

2.6. Quality Assessment and Risk of Bias

The methodological quality of eligible studies was evaluated using the appropriate Joanna Briggs Institute (JBI) critical appraisal tools for observational study designs, including cross-sectional, case-control, and cohort studies. The appraisal framework considered participant selection, measurement of transfusion exposure, antibody detection and outcome assessment, identification and management of potential confounding factors, and the appropriateness of statistical analyses. The appraisal findings were used to guide interpretation of the reliability and methodological limitations of the included evidence [33].

2.7. Data Synthesis and Analysis

Findings were synthesized narratively because of variations in underlying diagnoses, patient characteristics, transfusion exposure, antibody detection methods, and reported outcomes across the included studies.

Results were organized into structured evidence summaries addressing study characteristics, alloimmunization prevalence, predominant antibody specificities, associated risk factors, clinical consequences, and preventive transfusion strategies.

Reported prevalence estimates and measures of association were presented as documented in the original studies. Differences across clinical populations and geographical settings were examined descriptively, with particular attention to sickle cell disease, thalassemia, and other repeatedly transfused patient groups. A pooled prevalence estimate was not calculated, as differences in study populations, transfusion histories, and methodological approaches limited the suitability of quantitative pooling. Findings were interpreted with consideration of study design, sample size, clinical heterogeneity, and the limitations of the available evidence.

2.8. Ethical Considerations

This systematic review utilized data obtained exclusively from previously published studies and did not involve direct patient participation, intervention, or collection of identifiable personal information. Consequently, additional institutional ethical approval was not required for the review. Academic integrity was maintained through appropriate acknowledgment of original sources, accurate presentation of extracted findings, and transparent reporting of the study selection and evidence synthesis procedures.

3. Results

3.1. Study Selection

The systematic search across PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library identified 327 records. Following the removal of 42 duplicates, 285 records underwent title and abstract screening, of which 206 were excluded. Subsequently, 79 full-text reports were sought for retrieval, but five could not be obtained. Of the 74 reports assessed for eligibility, 37 were excluded, leaving 37 studies included in the final qualitative synthesis. The study identification, screening, eligibility assessment, and inclusion process is presented in the PRISMA 2020 flow diagram (Figure 1).

3.2. Characteristics of the Included Studies

The 37 included studies investigated red blood cell (RBC) alloimmunization among patients receiving repeated transfusions for sickle cell disease (SCD), transfusion-dependent thalassemia, myelodysplastic syndromes (MDS), chronic kidney disease (CKD), and other hematological conditions. The studies were conducted across Asia, Africa, Europe, the Middle East, and North America and employed cross-sectional, prospective observational, retrospective cohort, and multicenter designs. Considerable differences were observed in sample size, participant characteristics, cumulative transfusion exposure, and immunohematological testing procedures.

Most studies employed indirect antiglobulin testing, gel column agglutination, or solid-phase techniques for antibody screening and identification, while selected investigations incorporated extended RBC phenotyping or molecular genotyping to characterize Rh antigen variants and investigate alloimmunization despite conventional antigen matching [3, 13, 34, 35]. These methodological differences contributed to heterogeneity and limited direct comparisons of prevalence estimates across patient populations.

3.3. Prevalence of RBC Alloimmunization Across Patient Populations

The reported prevalence of RBC alloimmunization varied substantially across clinical populations and geographical settings. Among patients with thalassemia, prevalence ranged from 2.9% in Iran (Mobasheri et al., [36] to 32.5% in the United States [35]. Relatively low frequencies were reported in India, including 5.21%, Jain et al., [61], 5.64% Dhawan et al., [37], and 6.6% Yadav et al., [38]. Other studies reported 6.0% in Yemen Almorish et al., [39], 6.1% among pediatric patients in India Pradhan et al., [40], 8.5% in another Indian pediatric cohort, Dogra et al., [41], 12.6% in Palestine, Abu Taha et al., [42], 13.64% in India, Thakur et al., [43], and 18.0% in Egypt [44]. Higher frequencies were documented by Chaudhari [45] (18.8%) and Singer et al. [46] (22.0%). Abdelrazik et al. [47] reported an alloimmunization prevalence of approximately 7.98% among 188 multiply transfused patients with thalassemia in Egypt, further demonstrating geographical variation in alloimmunization frequencies across transfusion-dependent populations. In Thailand, Romphruk et al. [48] reported an alloimmunization frequency of approximately 19.3% among 383 patients with thalassemia, highlighting the substantial variation in antibody development among patients requiring repeated transfusions. Similarly, Teawtrakul et al. [49] documented an alloimmunization prevalence of 15.6% among 1,000 patients with transfusion-dependent thalassemia in a multicenter study conducted in Thailand, further illustrating differences in alloimmunization frequencies across clinical settings. Among patients with SCD, Solmaz et al. [50] reported alloimmunization in 31.0%, while Sins et al. [51], Kangiwa et al. [52], Rosse et al. [53], and Miller et al. [54] reported frequencies of 17.6%, 18.7%, 18.6%, and 14.4%, respectively. Comparative investigations demonstrated higher alloimmunization among patients with SCD than those with thalassemia, including 20.2% versus 4.6% in Bahrain, Altooq et al., [21] $p < 0.001$) and 10.9% versus 1.2% in India, Jariwala et al., [55] $p < 0.001$). Among other clinical populations, Sanz et al. [14] reported 15% among patients with MDS or chronic myelomonocytic leukemia, while Obi et al. [57] and John et al. [56] reported 3.2% and 7.1%, respectively, among previously transfused CKD patients. Ebreo et al. [58] identified alloimmunization in 18.2% of chronically transfused Filipino children with hematological disorders, whereas Bhuva and Vachhani [13] reported 3.0% among repeatedly transfused patients with mixed diagnoses.

These estimates were interpreted descriptively because several studies included patients with variable or incompletely characterized chronic transfusion exposure.

3.4. Distribution of RBC Alloantibody Specificities

Antibodies against the Rh and Kell blood group systems predominated across the included studies, particularly anti-E, anti-K, anti-C, anti-c, and anti-D, while antibodies against Kidd, Duffy, MNS, Lewis, and other systems were less frequently identified. Among patients with thalassemia, Dhawan et al. [37] reported that 52.17% of 23 identified alloantibodies belonged to the Rh system and approximately 35% to Kell. El-Beshlawy et al. [44] identified 86 alloantibodies, with anti-K accounting for 33.7% and Rh antibodies for 23.2%, while Almorish et al. [39] reported Kell and Rh antibodies in 41.2% and 29.4% of cases, respectively. Jain et al. [61] similarly identified Kell antibodies in four of five alloimmunized patients. Conversely, Waldis et al. [35] reported that 72.2% of identified alloantibodies belonged to the Rh system despite prophylactic antigen matching. Anti-E and anti-c were predominant in Chaudhari [45], while Dogra et al. [41] identified anti-E (50%), anti-K (33.3%), and anti-D (16.7%). Among patients with MDS or chronic myelomonocytic leukemia, Sanz et al. [14] identified 81 alloantibodies, predominantly involving Kell and Rh antigens, while Obi et al. [57] reported anti-E in all four alloimmunized CKD patients. Similar Rh and Kell predominance was observed among SCD and mixed hematological populations [52, 53, 58, 59, 62]. Consistent with these findings, Wilson et al. [64] reported that anti-K (37%) and anti-E (30%) were among the predominant alloantibody specificities identified in patients with hemoglobinopathies, reinforcing the importance of Rh and Kell blood group antigens in transfusion-related alloimmunization. Multiple antibody specificities were also documented, including 81 antibodies among 42 alloimmunized patients in Sanz et al. [14] and multiple antibodies in five of nine alloimmunized patients [43]. Bao et al. [65] similarly identified multiple alloantibodies among selected alloimmunized SCD patients.

3.5. Demographic, Clinical, and Transfusion-Related Risk Factors

Several studies identified cumulative transfusion exposure, age at initiation of transfusion therapy, splenectomy, and selected immunological characteristics as factors associated with RBC alloimmunization. Obi et al. [57] reported significantly greater transfusion exposure among alloimmunized CKD patients than among non-alloimmunized patients (17.5 ± 12 versus 6 ± 6 units; $p < 0.001$), while Yadav et al. [38] observed higher annual transfusion requirements among alloimmunized patients with thalassemia (median 30 versus 24 units; $p < 0.001$). Significant associations with transfusion frequency or duration were also reported by El-Beshlawy et al. [44], Sinha et al. [63] whereas Ebreo et al. [58], Abu Taha et al. [42], and Almorish et al. [39] reported no significant association.

Older age at first transfusion was associated with alloimmunization in Dhawan et al. [37] Yadav et al. [38] Pradhan et al. [40], and Sins et al. [51], although other studies reported no significant relationship. Splenectomy was associated with increased alloimmunization in Thompson et al. [20] (OR = 2.528; $p < 0.0001$), while Singer et al. [46] observed a higher but statistically nonsignificant frequency among splenectomized patients (36% versus 12.8%; $p = 0.06$). Associations involving age, sex, and ABO/Rh blood group characteristics were inconsistent across studies [39, 45, 56, 58]. Immunological investigations identified reduced regulatory T-cell suppressive activity among alloimmunized SCD patients Bao et al., [65]; $p < 0.05$), while Israelyan et al. [34] demonstrated an association between RHCE alleles encoding partial e antigens and anti-e formation ($p = 0.0007$). Collectively, the reported associations varied across study populations and were not sufficiently consistent to establish a uniform risk profile. Teawtrakul et al. [49] also identified older age, splenomegaly, and greater transfusion volume as factors associated with alloimmunization among patients with transfusion-dependent thalassemia. Wilson et al. [64] further reported a significant association between RhD-negative blood group status and alloimmunization ($p = 0.01$), suggesting that blood group characteristics may contribute to differences in alloantibody development.

3.6. Clinical Outcomes and Transfusion-Related Complications

RBC alloimmunization was associated with clinically relevant immunohematological challenges, including the formation of multiple alloantibodies, coexistence of autoantibodies, increased complexity of compatibility testing, and the potential need for antigen-negative blood. Singer et al. [46] identified erythrocyte autoantibodies in 25% of patients, including three cases of severe hemolytic anemia associated with autoimmunization. Similarly, Thompson et al. [20], Dhawan et al. [37] and El-Beshlawy et al. [44] reported autoantibody frequencies of 4.9%, 28.2%, and 16.5%, respectively. Multiple alloantibody formation was documented by Sanz et al. [14], Thakur et al. [43], and Bao et al. [65] while Sood et al. [3], Bhuva and Vachhani [13], and Handa et al. [59] described the provision of antigen-negative RBC units following antibody identification. However, relatively few studies directly quantified delayed hemolytic transfusion reactions, hyperhemolysis, transfusion delays, or difficulties obtaining compatible blood. Consequently, the evidence concerning long-term morbidity, mortality, and healthcare utilization remained limited.

3.7. Antigen-Matching and Antibody-Screening Strategies

The included studies evaluated routine antibody screening, extended RBC phenotyping, antigen-negative blood provision, and molecular approaches to antigen matching. Singer et al. [46] reported significantly lower alloimmunization among patients receiving extended Rh/Kell-matched blood than among those receiving standard ABO/RhD-matched transfusions (2.8% versus 33%; $p = 0.0005$), although differences in leukoreduction practices may have influenced the findings. Aldakheel et al. [60] also reported lower odds of alloimmunization with Rh–Kell phenotype matching (OR = 0.012; 95% CI: 0.001–0.11), while Sins et al. [51] observed a higher estimated risk with non-extended matching (HR = 2.0; 95% CI: 0.9–4.6), although the latter association was not statistically conclusive. Nevertheless, alloimmunization persisted despite prophylactic matching in some populations. Waldis et al. [35] reported alloimmunization in 32.5% of chronically transfused thalassemia patients receiving RhD-, C-, E-, and K-matched blood, while Israelyan et al. [34] documented institutional prevalence ranging from 5% to 41% among chronically transfused SCD patients. Routine antibody screening and the provision of antigen-negative blood were also described [3, 13, 59, 61]. However, few studies directly compared screening intervals or quantified the effects of alternative matching strategies on clinical outcomes.

3.8. Summary of Findings

The 37 included studies demonstrated substantial variation in RBC alloimmunization prevalence across repeatedly and chronically transfused populations. Rh and Kell antibodies were the predominant specificities, while transfusion exposure, age at first transfusion, splenectomy, and immunological or genetic characteristics showed variable associations with alloantibody formation. Although extended antigen matching was associated with reduced alloimmunization in some investigations, antibody development persisted despite preventive matching in others. Differences in study populations, transfusion histories, and laboratory methods, together with limited reporting of clinical outcomes, restricted direct comparisons and supported a descriptive rather than pooled quantitative synthesis.

4. Discussion

This systematic review synthesized evidence from 37 studies examining the prevalence, alloantibody specificities, associated risk factors, clinical outcomes, and preventive strategies related to red blood cell (RBC) alloimmunization among chronically and repeatedly transfused patients. The findings revealed considerable variation in alloimmunization prevalence across patient populations and geographical settings, with differences in underlying diseases, transfusion exposure, donor–recipient antigen compatibility, and immunohematological practices potentially contributing to this heterogeneity.

4.1. Prevalence of RBC Alloimmunization

The substantial variation in alloimmunization prevalence highlights the complexity of immune sensitization following repeated RBC transfusions.

Lower frequencies were reported by Mobasheri et al. [36], [13], and Dhawan et al. [37] whereas considerably higher rates were documented by Solmaz et al. [50], and Waldis et al. [35]. These differences suggest that cumulative transfusion exposure alone may not adequately explain alloimmunization risk. Underlying hematological conditions, recipient immunological characteristics, antigenic differences between donors and recipients, and the extent of prophylactic antigen matching may also contribute. The relatively high alloimmunization frequencies observed in several sickle cell disease cohorts, compared with some thalassemia populations, further suggest disease-related differences in immune responses and transfusion practices [20, 21, 55]. Nevertheless, differences in study design, transfusion history, and patient selection limit direct comparisons and prevent definitive conclusions regarding disease-specific risk.

4.2. Alloantibody Specificities

The predominance of antibodies against the Rh and Kell blood group systems was one of the most consistent findings across the included studies. Anti-E, anti-K, anti-C, and anti-c were frequently reported, although their distributions differed across clinical populations and geographical regions [14, 37, 39, 44]. This pattern suggests that donor–recipient antigen disparities remain important contributors to alloantibody formation. Furthermore, the occurrence of multiple alloantibodies in some patients emphasizes the increasing complexity of transfusion compatibility management following repeated antigen exposure. These findings provide support for extended Rh and Kell antigen matching, particularly among individuals requiring prolonged transfusion therapy. However, the persistence of alloimmunization despite conventional antigen matching, as observed by Waldis et al. [35] and Israelyan et al. [34], indicates that additional antigenic and genetic factors may influence antibody development.

4.3. Risk Factors Associated With Alloimmunization

Cumulative transfusion exposure, age at first transfusion, and splenectomy emerged as potentially important factors associated with alloimmunization, although their relationships were inconsistent across studies. Increased transfusion exposure was associated with alloantibody development in investigations involving chronic kidney disease and thalassemia (Obi et al., [57] Yadav et al.,[38], while other studies reported no statistically significant association [39, 42]. Similarly, older age at transfusion initiation was associated with alloimmunization in selected cohorts [37] Sins et al., [51] Pradhan et al., [40], and splenectomy was identified as a significant risk factor by Thompson et al. [20]. However, these findings were not consistently replicated. The observed variability suggests that alloimmunization results from interactions among transfusion exposure, underlying disease, recipient immune responsiveness, and antigen compatibility rather than a single determining factor.

Immunological and molecular findings reported by Bao et al. [65] and Israelyan et al. [34] further indicate that individual immune regulation and Rh genetic variation may contribute to susceptibility.

4.4. Clinical Implications and Preventive Strategies

RBC alloimmunization has important implications for transfusion safety because clinically significant alloantibodies can complicate compatibility testing, restrict access to suitable blood components, and increase the potential for hemolytic transfusion reactions. The coexistence of alloantibodies and autoantibodies reported in several studies may further complicate patient management, particularly among individuals requiring lifelong transfusion support [37, 44]. However, the limited reporting of directly observed clinical complications prevents a comprehensive assessment of the long-term consequences of alloimmunization. Preventive approaches, particularly extended antigen matching, demonstrated favorable associations in selected studies. Singer et al. [46] reported substantially lower alloimmunization among patients receiving extended Rh/Kell-matched RBC units, although differences in leukoreduction practices may have influenced the observed association. Similarly, evidence from other investigations suggests potential benefits of antigen matching, but the persistence of alloimmunization despite prophylactic matching indicates that conventional strategies may not eliminate risk [35, 51]. These findings support individualized transfusion planning, routine antibody screening, accurate documentation of historical antibodies, and consideration of expanded antigen matching where resources permit.

4.5. Limitations of the Evidence

The interpretation of these findings is limited by substantial clinical and methodological heterogeneity among the included studies. Differences in sample size, underlying diagnoses, transfusion histories, study designs, antibody detection techniques, and antigen-matching protocols restricted direct comparisons of alloimmunization prevalence and associated risk factors. Some investigations included mixed transfusion populations or did not clearly distinguish chronically transfused patients from those receiving occasional transfusions, further limiting generalizability. Additionally, the predominance of observational and single-center studies, inconsistent adjustment for confounding variables, and limited reporting of long-term clinical outcomes reduced the strength of conclusions regarding causality and preventive effectiveness. Consequently, the findings were synthesized descriptively rather than through quantitative pooling.

This review demonstrates that RBC alloimmunization remains a clinically important complication of repeated transfusion therapy.`

The predominance of Rh and Kell antibodies, together with the variable associations observed for transfusion exposure, age at first transfusion, splenectomy, and immunological characteristics, underscores the multifactorial nature of alloantibody development. Although extended antigen matching and systematic antibody screening offer important preventive approaches, further high-quality comparative research is required to establish their effectiveness across different clinical populations and healthcare settings.

Table 1: Characteristics of the 37 Included Studies

Study	Country/region	Population	N	Design (summary)
Sood et al. (2013)	India	Mixed	306	Observational
Bhuva and Vachhani (2017)	India	Mixed	300	Prospective observational
Thompson et al. (2011)	North America/UK	Thalassemia	697	Multicenter observational
Sanz et al. (2012)	Not specified	MDS/CMML	272	Retrospective cohort
Israelyan et al. (2024)	United States	SCD	342	Multicenter cohort
Obi et al. (2018)	Nigeria	CKD	124	Observational
Singer et al. (2000)	United States	Thalassemia	64	Observational
Sins et al. (2016)	Netherlands	SCD	245	Observational
Bao et al. (2011)	United States	SCD/thalassemia	30	Immunological case comparison
Ebreo et al. (2021)	Philippines	Pediatric hematologic	55	Observational
Dhawan et al. (2014)	India	Thalassemia	319	Observational
John et al. (2025)	Uganda	CKD	141	Observational
Altooq et al. (2026)	Bahrain	SCD and thalassemia	311	Observational
Yusuf et al. (2025)	Saudi Arabia	SCD	241	Observational
Sinha et al. (2026)	India	Mixed	100	Observational
Solmaz et al. (2016)	Turkey	SCD	216	Observational
Miller et al. (2013)	United States	SCD	237	Feasibility cohort
Waldis et al. (2021)	United States	Thalassemia	40	Observational/molecular
Abu Taha et al. (2019)	Palestine	Thalassemia	215	Observational
Kangiwa et al. (2015)	Nigeria	SCD	80	Observational
Jain et al. (2014)	India	Thalassemia	96	Observational
El-Beshlawy et al. (2020)	Egypt	Thalassemia	200	Observational
Almorish et al. (2024)	Yemen	Thalassemia	100	Observational
Chaudhari (2011)	India	Thalassemia	32	Observational
Yadav et al. (2023)	India	Thalassemia	255	Observational
Dogra et al. (2015)	India	Thalassemia	70	Observational
Handa et al. (2020)	India	Mixed	100	Prospective follow-up
Rosse et al. (1990)	United States	SCD	1,814	Multicenter observational
Jariwala et al. (2019)	India	SCD and thalassemia	471	Observational
Mobasheri et al. (2022)	Iran	Thalassemia	68	Observational
Thakur et al. (2023)	India	Thalassemia	66	Observational
Abdelrazik et al. (2016)	Egypt	Thalassemia	188	Observational
Teawtrakul et al. (2022)	Thailand	Thalassemia	1,000	Multicenter registry
Romphruk et al. (2019)	Thailand	Thalassemia	383	Retrospective observational
Wilson et al. (2023)	Egypt	Thalassemia/SCD	200	Observational
Pradhan et al. (2025)	India	Pediatric thalassemia	82	Observational
Aldakheel et al. (2022)	Saudi Arabia	SCD	246	Observational

Note. *Study designs are broad descriptions based on supplied summaries; exact design labels require article-level confirmation. Some cohorts contain episodically transfused participants.*

Table 2: Reported RBC Alloimmunization Frequencies

Study	Population	Total N	Alloimmunized n	Reported frequency
Sood et al. (2013)	Mixed	306	≈13	4.24%
Bhuva and Vachhani (2017)	Mixed	300	9	3.0%
Thompson et al. (2011)	Thalassemia	697	115	16.5%
Sanz et al. (2012)	MDS/CMML	272	42	15%
Israelyan et al. (2024)	SCD	342	NR	5–41% by center
Obi et al. (2018)	CKD	124	4	3.2%
Singer et al. (2000)	Thalassemia	64	14	22%
Sins et al. (2016)	SCD	245	43	17.6%
Bao et al. (2011)	SCD/thalassemia	30	Selected cases	Not estimable
Ebreo et al. (2021)	Pediatric hematologic	55	10	18.2%
Dhawan et al. (2014)	Thalassemia	319	18	5.64%
John et al. (2025)	CKD	141	10	7.1%
Altooq et al. (2026)	SCD and thalassemia	311	46	14.8% overall
Yusuf et al. (2025)	SCD	241	NR	NR
Sinha et al. (2026)	Mixed	100	14	14%

Solmaz et al. (2016)	SCD	216	67	31.0%
Miller et al. (2013)	SCD	237	34	14.4%
Waldis et al. (2021)	Thalassemia	40	13	32.5%
Abu Taha et al. (2019)	Thalassemia	215	NR	12.6%
Kangiwa et al. (2015)	SCD	80	15	18.7%
Jain et al. (2014)	Thalassemia	96	5	5.21%
El-Beshlawy et al. (2020)	Thalassemia	200	36	18%
Almorish et al. (2024)	Thalassemia	100	6	6%
Chaudhari (2011)	Thalassemia	32	6	18.8%
Yadav et al. (2023)	Thalassemia	255	17	6.6%
Dogra et al. (2015)	Thalassemia	70	6	8.5%
Handa et al. (2020)	Mixed	100	7 new	7% incident
Rosse et al. (1990)	SCD	1,814	NR	18.6%
Jariwala et al. (2019)	SCD and thalassemia	471	19	10.9% SCD; 1.2% thal
Mobasheri et al. (2022)	Thalassemia	68	2	2.9%
Thakur et al. (2023)	Thalassemia	66	9	13.64%
Abdelrazik et al. (2016)	Thalassemia	188	≈15	7.98%
Teawtrakul et al. (2022)	Thalassemia	1,000	156	15.6%
Romphruk et al. (2019)	Thalassemia	383	≈74	19.3%
Wilson et al. (2023)	Thalassemia/SCD	200	22	11.0%
Pradhan et al. (2025)	Pediatric thalassemia	82	5	6.1%
Aldakheel et al. (2022)	SCD	246	NR	Discrepant; verify

Note. *Rates reflect each study's reported denominator and are not directly comparable. Handa et al. report new antibody development, not baseline prevalence. Israelyan et al. provide center-specific range. Bao et al. used selected cases. Aldakheel et al. requires reconciliation of inconsistent reported estimates.*

Table 3: Reported RBC Alloantibody Specificities

Study	Reported specificity / distribution	Interpretive category
Sood et al. (2013)	NR in extracted summary table	Not specified
Bhuva and Vachhani (2017)	NR in extracted summary table	Not specified
Thompson et al. (2011)	NR	Not specified
Sanz et al. (2012)	Kell; anti-E, anti-c, anti-Jk^a	Rh/Kell
Israelyan et al. (2024)	NR in extracted summary table	Not specified
Obi et al. (2018)	Anti-E	Rh/Kell
Singer et al. (2000)	NR	Not specified
Sins et al. (2016)	NR in extracted summary table	Not specified
Bao et al. (2011)	Multiple antibodies in selected SCD cases	Not specified
Ebreo et al. (2021)	Anti-E	Rh/Kell
Dhawan et al. (2014)	Rh (52.17%); Kell (~35%)	Rh/Kell
John et al. (2025)	Anti-K	Not specified
Altooq et al. (2026)	NR in extracted summary table	Not specified
Yusuf et al. (2025)	NR in extracted summary table	Not specified
Sinha et al. (2026)	NR in extracted summary table	Not specified
Solmaz et al. (2016)	NR in extracted summary table	Not specified
Miller et al. (2013)	NR in extracted summary table	Not specified
Waldis et al. (2021)	Rh (13/18 antibodies)	Rh/Kell
Abu Taha et al. (2019)	NR in extracted summary table	Not specified
Kangiwa et al. (2015)	NR in extracted summary table	Not specified
Jain et al. (2014)	Kell (4/5 patients)	Rh/Kell
El-Beshlawy et al. (2020)	Anti-K (33.7%); Rh (23.2%)	Rh/Kell
Almorish et al. (2024)	Kell (41.2%); Rh (29.4%)	Rh/Kell
Chaudhari (2011)	Anti-E; anti-c	Rh/Kell
Yadav et al. (2023)	NR in extracted summary table	Not specified
Dogra et al. (2015)	Anti-E; anti-K; anti-D	Rh/Kell
Handa et al. (2020)	NR in extracted summary table	Not specified
Rosse et al. (1990)	NR in extracted summary table	Not specified
Jariwala et al. (2019)	NR in extracted summary table	Not specified
Mobasheri et al. (2022)	Anti-K; anti-C; anti-E	Rh/Kell
Thakur et al. (2023)	Anti-K; anti-Kp^a; anti-C; anti-C^w	Rh/Kell
Abdelrazik et al. (2016)	Anti-D; anti-C; anti-E; anti-c; anti-Fy^a; anti-K	Rh/Kell
Teawtrakul et al. (2022)	Anti-E; anti-Mi^a; anti-c	Rh/Kell
Romphruk et al. (2019)	Anti-E; anti-Mi^a; anti-c	Rh/Kell
Wilson et al. (2023)	Anti-K (37%); anti-E (30%)	Rh/Kell
Pradhan et al. (2025)	NR in extracted summary table	Not specified
Aldakheel et al. (2022)	NR in extracted summary table	Not specified

Note. *NR indicates no specific entry was reliably transcribed into this table; it does not imply that the original study reported no antibodies. Percentages may use antibody detections rather than patient counts as denominators.*

Table 4: Factors Associated With RBC Alloimmunization

Study	Selected reported risk-factor finding	Evidence status
Sood et al. (2013)	Not reliably extractable	NR
Bhuva and Vachhani (2017)	Not reliably extractable	NR
Thompson et al. (2011)	Splenectomy OR 2.528; p < .0001	Reported association
Sanz et al. (2012)	Not reliably extractable	NR
Israelyan et al. (2024)	RHCE partial-e allele associated with anti-e; p = .0007	Reported association
Obi et al. (2018)	Higher RBC exposure (17.5 ± 12 vs 6 ± 6 units); p < .001	Reported association
Singer et al. (2000)	Splenectomy 36% vs 12.8%; p = .06 (NS)	Reported association
Sins et al. (2016)	Age at first transfusion ⩾5 years: HR 2.3 (95% CI 1.0–5.1)	Reported association
Bao et al. (2011)	Lower regulatory T-cell suppressive activity; p < .05	Reported association
Ebreo et al. (2021)	Not reliably extractable	NR
Dhawan et al. (2014)	Older age at first transfusion associated; p = .042	Reported association
John et al. (2025)	Not reliably extractable	NR
Altooq et al. (2026)	Not reliably extractable	NR
Yusuf et al. (2025)	Not reliably extractable	NR
Sinha et al. (2026)	Transfusion exposure associated (effect estimate NR)	Reported association
Solmaz et al. (2016)	Not reliably extractable	NR
Miller et al. (2013)	Not reliably extractable	NR
Waldis et al. (2021)	Not reliably extractable	NR
Abu Taha et al. (2019)	No significant exposure association	Reported association
Kangiwa et al. (2015)	Not reliably extractable	NR
Jain et al. (2014)	Not reliably extractable	NR
El-Beshlawy et al. (2020)	Transfusion frequency/duration associated (estimate NR)	Reported association
Almorish et al. (2024)	Age/sex associations; p = .013/.030	Reported association
Chaudhari (2011)	Not reliably extractable	NR
Yadav et al. (2023)	Higher annual RBC units (median 30 vs 24); p < .001	Reported association
Dogra et al. (2015)	Not reliably extractable	NR
Handa et al. (2020)	Not reliably extractable	NR
Rosse et al. (1990)	Not reliably extractable	NR
Jariwala et al. (2019)	Not reliably extractable	NR
Mobasheri et al. (2022)	Not reliably extractable	NR
Thakur et al. (2023)	Transfusion burden, splenectomy, age associations; estimates NR	Reported association
Abdelrazik et al. (2016)	Not reliably extractable	NR
Teawtrakul et al. (2022)	Age ⩾3 years, splenomegaly, greater transfusion volume associated; estimates NR	Reported association
Romphruk et al. (2019)	Splenectomy and higher transfusion exposure associated; estimates NR	Reported association
Wilson et al. (2023)	RhD-negative status associated; p = .01	Reported association
Pradhan et al. (2025)	Transfusion initiation after age 1: OR 1.42 (95% CI 1.36–1.49); p = .02	Reported association
Aldakheel et al. (2022)	Not reliably extractable	NR

Note. *Only selected directly reported associations are tabulated. NS = not statistically significant. "Not reliably extractable" is not evidence of no association. Avoid interpreting unadjusted associations as causal.*

Table 5: Clinical Outcomes and Preventive Transfusion Practices

Study	Reported outcome or practice	Type of evidence
Sood et al. (2013)	Antigen-negative RBC units supplied after detection	Descriptive / NR
Bhuva and Vachhani (2017)	Antigen-negative units supplied; no new antibodies in follow-up	Descriptive / NR
Thompson et al. (2011)	Autoantibodies 34/697 (4.9%)	Descriptive / NR
Sanz et al. (2012)	Multiple antibodies (81 in 42 patients)	Descriptive / NR
Israelyan et al. (2024)	Alloimmunization despite matching; Rh variants implicated	Descriptive / NR
Obi et al. (2018)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Singer et al. (2000)	Autoantibodies 16/64 (25%); 3 severe hemolytic anemia cases; extended matching 2.8% vs 33%	Comparative evidence
Sins et al. (2016)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Bao et al. (2011)	Multiple antibodies in selected cases	Descriptive / NR
Ebreo et al. (2021)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Dhawan et al. (2014)	Autoantibodies 90/319 (28.2%)	Descriptive / NR
John et al. (2025)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Altooq et al. (2026)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Yusuf et al. (2025)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Sinha et al. (2026)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Solmaz et al. (2016)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Miller et al. (2013)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Waldis et al. (2021)	Alloimmunization 32.5% despite RhD/C/E/K matching	Comparative evidence
Abu Taha et al. (2019)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Kangiwa et al. (2015)	Clinical outcome / preventive comparison not quantified	Descriptive / NR

Jain et al. (2014)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
El-Beshlawy et al. (2020)	Autoantibodies 33/200 (16.5%)	Descriptive / NR
Almorish et al. (2024)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Chaudhari (2011)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Yadav et al. (2023)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Dogra et al. (2015)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Handa et al. (2020)	New antibodies over 12 months; antigen-negative RBCs	Descriptive / NR
Rosse et al. (1990)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Jariwala et al. (2019)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Mobasheri et al. (2022)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Thakur et al. (2023)	Multiple specificities in 5/9 alloimmunized	Descriptive / NR
Abdelrazik et al. (2016)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Teawtrakul et al. (2022)	Other transfusion complications reported, not attributable to alloimmunization	Descriptive / NR
Romphruk et al. (2019)	Autoantibodies 9/383 (2.3%); extended matching evaluated	Descriptive / NR
Wilson et al. (2023)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Pradhan et al. (2025)	Clinical outcome / preventive comparison not quantified	Descriptive / NR
Aldakheel et al. (2022)	Rh/Kell matching association; prevalence figures inconsistent	Comparative evidence

Note. *Autoimmunization is distinct from alloimmunization. Other transfusion reactions cannot automatically be attributed to RBC alloantibodies. NR does not mean an outcome was absent.*

5. Conclusion

This systematic review of 37 studies demonstrates considerable variation in the prevalence of RBC alloimmunization among chronically and repeatedly transfused patients, particularly those with sickle cell disease and thalassemia. Antibodies against the Rh and Kell blood group systems were the most frequently identified, while cumulative transfusion exposure, age at first transfusion, splenectomy, and individual immunological characteristics emerged as potential risk factors, although associations were inconsistent across studies. Alloimmunization presents important challenges for transfusion compatibility and patient safety, but evidence regarding its long-term clinical consequences remains limited. The findings support regular antibody screening, appropriate antigen matching, comprehensive transfusion records, and individualized transfusion management, while emphasizing the need for further research to strengthen evidence-based preventive strategies.

6. Recommendations

Based on the findings of this systematic review, the following recommendations are proposed:

1. Extended antigen matching: Rh (C, c, E, e) and Kell antigen matching should be considered for patients requiring long-term RBC transfusions, particularly those with previous alloimmunization or increased transfusion requirements, where feasible.

2. Routine antibody screening: Regular pretransfusion antibody screening and identification should be performed in accordance with established transfusion guidelines to facilitate early detection of clinically significant alloantibodies.

3. Individualized transfusion management: Transfusion strategies should consider patients' underlying diagnoses, transfusion histories, previous antibody formation, and relevant clinical risk factors to improve compatibility and minimize transfusion-related complications.

4. Comprehensive transfusion documentation: Healthcare institutions should maintain accurate and accessible records of transfusion exposure, historical antibodies, antigen profiles, and adverse transfusion reactions to support safe and timely blood provision.

5. Further research: Large, multicenter prospective studies with standardized definitions, laboratory methods, and outcome measures are recommended to clarify alloimmunization risk factors, evaluate long-term clinical consequences, and determine the effectiveness and cost-effectiveness of extended and molecular antigen-matching strategies.

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