Alloimmunisation against red blood cells in sickle cell disease: transfusion challenges in high-income and low-income countries

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Sickle cell disease is the most frequent inherited disorder in sub-Saharan Africa and in many high-income countries (HICs). Transfusion is a key element of treatment, but it results in high rates of alloimmunisation against red blood cell antigens and post-transfusion haemolysis, which can be life-threatening in severe cases. The prevention of alloimmunisation is, therefore, an important issue in both HICs and in low-income countries (LICs). In HICs, the main reason for high alloimmunisation rates is blood group disparity between blood donors, who are mostly of European descent, and the patients, who are mostly of African descent. However, alloimmunisation rates also remain high in sub-Saharan Africa despite the homogeneity of blood group antigen frequencies between donors and patients; this occurrence is probably due to matching strategies limited to ABO blood group and RhD. However, other possible underlying causes of alloimmunisation have also been suggested, with each cause affecting HICs and LICs in different ways—eg, the immunogenetic and inflammatory status of the patient and the characteristics of the red blood cell products. In this Viewpoint, we discuss the available data and hypotheses that potentially account for the association of sickle cell disease with high rates of alloimmunisation in both settings, HICs and LICs (focusing particularly on sub-Saharan Africa), and the challenges faced by HICs and LICs to improve prevention of alloimmunisation.

Introduction

Sickle cell disease is the most common inherited red blood cell disorder in sub-Saharan Africa.[1] Sickle cell disease is also common in Black populations in the USA and, due to migration of populations from countries with a high prevalence of sickle cell disease over the past 50 years, it is also common in populations of African descent in Europe. Sickle cell disease is the most common inherited disease in France, where there are about 30 000 people living with the condition.[2] In sickle cell disease, haemoglobin is altered, which leads to anaemia, altered blood flow in the body with vaso-occlusive crises, and progressive multiorgan failure.

Transfusion therapy holds a major place for people with sickle cell disease. The replacement of red blood cells carrying the sickle cell form of haemoglobin (HbS) with red blood cells carrying the healthy form of haemoglobin (HbA) not only treats acute symptoms, but also prevents strokes and reduces the occurrence of crises by ensuring that HbS concentrations remain at acceptable levels in people with the condition. However, transfusion can provoke severe adverse effects due to the development of alloantibodies against red blood cell antigens, and life-threatening haemolytic transfusion reactions due to the reactivation of previously formed antibodies.[3] Alloimmunisation can also make it difficult to obtain phenotypically matched compatible red blood cells for subsequent transfusions. In high-income countries (HICs), alloimmunisation is particularly common in people with sickle cell disease, due at least partly to blood group differences between the donors, who are mostly of European descent, and the patients, who are of African descent. One systematic review of HICs reported alloimmunisation rates as high as 47%, depending on the extent of blood group matching.[4] Incidences of alloimmunisation are lower in sub-Saharan Africa than in most HICs. In a systematic review in sub-Saharan Africa, the overall incidence of alloimmunisation was 7·4% but reached 28·0% in some countries, despite blood group similarities between donors and recipients.[5] However, alloimmunisation incidence might have been underestimated in these studies from sub- Saharan Africa because antibody-screening tests are rarely performed in low-income countries (LICs) and, therefore, evanescent antibodies (ie, antibodies that are developed after stimulation, but then disappear from the plasma and cannot be detected anymore) developed in the past might not have been taken into account, as it is the case of most studies from HICs. Other factors play a role in alloimmunisation incidence in both HICs and LICs, and some of these factors are associated with the pathophysiology of the disease. Differences in medical practice and the environment (ie, country, customs, and health-care system) might also have an effect in both settings.

Despite the large number of studies done on the mechanisms of alloimmunisation, including the effect of biohazard substances released in red blood cell concentrates and the effect of the clinical, biological, and genetic status of patients, there are still too few bench-to-bedside applications. The routine prevention of alloimmunisation still consists exclusively of the selection of red blood cells for various numbers of antigens, to prevent the exposure of patients to blood group antigens not expressed by their own red blood cells. However, this selection has benefited from extensive serological and molecular investigations of blood groups. For example, Rh antigen variants associated with alloimmunisation are

investigated by genotyping and are considered in some matching strategies.[6] In HICs, international guidelines[7] are applied, including a number of measures for preventing alloimmunisation and its consequences. By contrast, LICs, particularly in sub-Saharan Africa, face difficulties in terms of access to phenotype-matched products, analyses, and patient follow-up.[1,8]

In this Viewpoint, we review the available data and hypotheses that potentially account for the association of sickle cell disease with high rates of alloimmunisation in HICs and LICs. We then consider the challenges currently faced in both settings to improve prevention of alloimmunisation.

Risk factors for alloimmunisation and their effect in HICs and LICs

Differences between donor and patient red blood cell antigens

Some polymorphic blood group antigens (eg, C and E, Fy^a, Fy^b, Jk^b, and S) are much less frequently expressed in patients of African descent than in donors of European descent, resulting in high alloimmunisation rates in HICs, where the donor population is predominantly of European descent. In HICs, prophylactic matching for ABO, RhD, C, c, E, e, and K and is widespread, with possible extended matching for Jk^a, Jk^b, Fy^a, Fy^b, S, and s in immunised patients. In contrast, matching in LICs is often limited to ABO and RhD. This matching is one of the reasons for the high levels of alloimmunisation observed in sub-Saharan Africa, with many anti-Rh and anti-Kell antibodies resulting from Rh and Kell differences between donors and recipients, despite the overall higher level of similarity of blood groups among African patients compared with patients transfused in HICs (figure 1).[5]

A second cause of alloimmunisation in both HICs and LICs is the extremely broad range of genetic diversity of *RH* genes in individuals of African descent, some of whom produce so-called partial antigens, which do not possess certain immunogenic epitopes.[9] Partial antigens can be deduced reliably only by *RH* genotyping, as routine serological techniques are not sensitive enough to differentiate between conventional and partial antigens. Carriers of partial antigens who are exposed to conventional Rh proteins might produce antibodies against the epitopes that are absent from their own incomplete Rh proteins. This situation explains the high frequency of anti-Rh antibodies produced in patients that seem to express the protein (eg, anti-D antibodies in an individual testing positive for D by serology). In 2018, a survey of people with sickle cell disease in France revealed that 253 (22%) of 1148 tested individuals had at least one partial Rh antigen, as deduced by genotyping.[10] In HICs, Rh variants have become a key issue in matching strategies for people with sickle cell disease.[6] Meanwhile, there is little data in LICs on the alloimmunisation effect of these same variants.

Key messages

- People with sickle cell disease have the highest rate of alloimmunisation of all patients undergoing blood transfusion
- Alloimmunisation against red blood cell antigens in sickle cell disease results primarily from blood group differences between donors and recipients
- In high-income countries there are major disparities in blood group antigen frequencies between the donors (typically of European descent) and the patients (typically of African descent); therefore, there is a need to encourage the minority population who are of African descent to donate blood
- In low-income countries, particularly in sub-Saharan Africa, there are smaller disparities in blood group antigen frequencies (both the patients and donors are mostly of African descent), but matching strategies should be upgraded to take into account the most immunogenic blood group antigens
- Apart from blood group, other factors affect alloimmunisation in people with sickle cell disease—ie, the inflammatory status and immunogenetic characteristics of the patient, and probably the manufacturing, storage, and components of red blood cell units, with different effects in low-income countries and high-income countries
- Further studies are required to determine the contributions of potential risk factors for alloimmunisation, so that bench-to-bedside applications can be developed based on alloimmunisation studies done in animal models and in vitro

High-frequency antigens are a group of antigens expressed by almost every person globally, with the exception of a small proportion of the world population. The absence of high-frequency antigens characterises many rare blood phenotypes. Some high-frequency antigens are absent only in individuals of African descent (eg, U–, HrS–, HrB–, Sec–, CEVF–).[11] Transfusion exposes rare phenotype carriers to the high-frequency antigens, with a variable risk of antibody development, resulting in the absence of compatible red blood cells for future transfusions. Transfusion of patients with rare blood types is an issue both in LICs, where rare blood types are not investigated in donors or patients, and in HICs, because, even when serological and molecular tools are available, donors with these rare phenotypes that are found only in individuals of African descent remain too rare among the population of blood donors and are unable to meet demand.

Finally, some antigens are expressed only in individuals of African descent (eg, V, VS, D^W, Go^a, MNS6, Js^a)[11] and are, therefore, considered to be low-frequency antigens in individuals of European descent. Anti-low-frequency antigens can be produced when patients of African descent receive red blood cells from donors of the same origin,

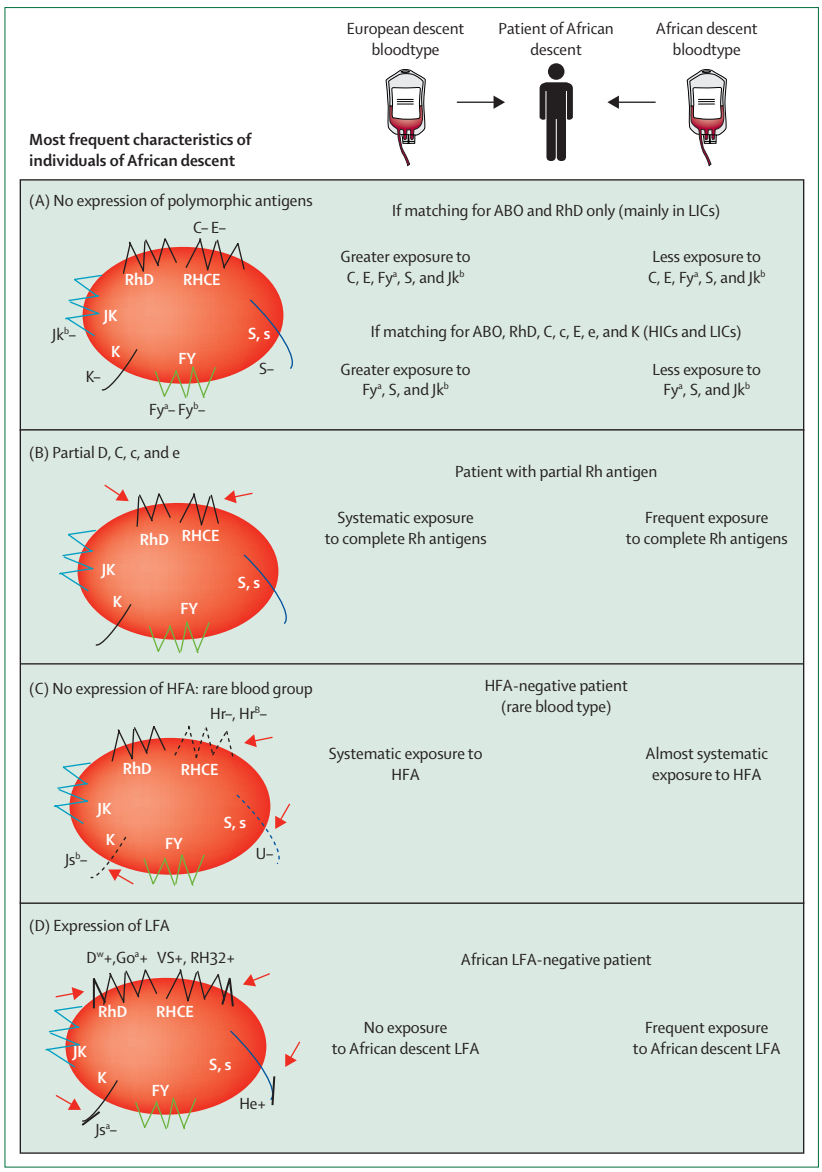

Figure 1: **Red blood cell antigen exposure in patients receiving red blood cells from donors of European or African descent**

Characteristics of red blood cell antigens in individuals of African descent. (A) Common antigens, (B) partial antigens, (C) non-expressed HFA (dotted), (D) expressed LFA (bold). In each case, the antigen exposure of the patient of African descent is shown according to donor origin. HFA=high-frequency antigen. HIC=high-income country. LFA=low-frequency antigen. LIC=low-income country. RHCE=Rh blood group CcEe antigens.

which is most often the case in sub-Saharan Africa, but might also occur in HICs when blood from donors of African descent is selected to ensure closer phenotype matching. Low-frequency antigens are rarely expressed on the red blood cells used for pretransfusion antibody-screening tests, as these red blood cells are generally obtained mostly from donors of European descent in HICs. Pretransfusion serological crossmatching (testing of the patient's plasma against a sample of the selected red blood cell unit), which is frequently the only pretransfusion test performed in sub-Saharan Africa, can reveal incompatibilities due to the presence of anti-low-frequency antigen antibodies, provided that these antibodies are not evanescent.[12,13]

Sickle cell disease promotes alloimmunisation

Despite close matching of blood groups, through genotyping in HICs or due to the similar blood groups of patients and donors in sub-Saharan Africa, people with sickle cell disease have the highest rates of alloimmunisation of all patients undergoing transfusion, with incidences of 47%—and even higher—reported in some studies.[4,14] By comparison, one study from 2022 reported a maximum incidence of 10% for alloimmunisation in patients with myelodysplastic syndrome.[15] Sickle cell disease is characterised by substantial inflammation, which is accentuated during acute crises, probably due to the effects of free haem, free haemoglobin, mitochondrial DNA, and the pro-inflammatory C3a and C5b released during increased complement activation in sickle cell disease, and also induced by cell-free HbS.[16–20] Inflammation is also a known risk factor for alloimmunisation against red blood cells, as shown in murine models and in people with sickle cell disease.[21,22] It is possible that the higher frequency of childhood infectious diseases reported in LICs compared with that in HICs results in greater inflammation in these patients, offsetting the benefit of the similarity of blood groups between donors and recipients.[23] In addition to this inflammation-driven effect, the constant release of haem in people with sickle cell disease might also modulate immune cells and alloimmunisation.[24]

Given the growing evidence that inflammation plays a key role in alloimmunisation, and that many bioactive substances can increase inflammation in people with sickle cell disease, the development of novel treatments for sickle cell disease that target free haemoglobin, complement activation, and inflammation would be expected to decrease alloimmunisation rates. For example, tocilizumab (an anti-IL-6 receptor antibody) was shown to be effective for the treatment of acute chest syndrome unrelated to COVID-19 in a 6-year-old child with sickle cell disease.[25] The target of this antibody, the IL-6 receptor, has been shown to modulate alloimmunisation in mice.[26] The use of this treatment to manage severe haemolytic transfusion reactions has been reported in a published case report.[27] These findings raise questions about the potential value and cost–benefit ratio of the preventive use of anti-inflammatory drugs before transfusion in patients at high risk of developing antibodies and haemolysis.

Other patient characteristics: age and number of previous transfusions

In HICs, alloimmunisation rates are lower in children (aged <15 years) with sickle cell disease than in adults (aged ≥18 years).[28] These lower alloimmunisation rates

probably reflect the use of red blood cells matched for ABO, RhD, C, c, E, e, and K in patients in HICs, right from the first transfusion, whereas no such matching is performed in LICs. Age at first transfusion can also influence the risk of alloimmunisation, with patients aged 5 years and older at the time of first transfusion significantly more likely to produce antibodies in HICs.[29] Studies in mice have shown that transfusion in the absence of inflammation induces antigen-specific tolerance to red blood cell antigens.[30] It is tempting to extrapolate these data in children with sickle cell disease, who often benefit from chronic transfusion protocols for stroke prevention in HICs. In chronically transfused children, inflammation is lower than in acute conditions, and transfusion can promote tolerance to subsequent transfusion. In sub-Saharan Africa, the mean age of patients is lower than in HICs[31] and patients mostly undergo transfusion for acute events, which might at least partly account for the maintenance of high rates of alloimmunisation, although this remains to be definitively shown.

Another reason for the higher rates of alloimmunisation in adults than in children, and also in HICs than in LICs, is the number of exposures to transfusion and, consequently, the likelihood of exposure to red blood cell antigens absent from the patient's own red blood cells. The number of red blood cell units received per patient increases with age, especially in HICs, where transfusion is more readily available.

Characteristics of donors and blood products

Bioactive substances can be released and accumulated during storage, and some of these substances, such as free haemoglobin, cytokines, and microparticles, can have pro-inflammatory effects, modulating the immune cells involved in alloimmunisation.[16,32] In 2022, it was shown in a murine model that the reticulocyte content of the product transfused could affect alloimmunisation rates, probably due to the presence of damage-associated molecular patterns, such as mitochondrial DNA.[33]

Donor characteristics, such as heterozygosity for HbS (ie, sickle cell trait) or G6PD deficiency in individuals of African descent can also potentiate alloimmunisation in the recipient. G6PD-deficient blood concentrates have been shown to be associated with increased rates of haemolysis and worse post-transfusion recovery.[34,35] Red blood cells from donors with sickle cell trait can have an inflammatory effect if free HbS is released into the product, especially in LICs where the incidence of sickle cell trait can reach 12% in some sub-Saharan countries.[36] In HICs, the strategy of sickle cell trait detection in donors of African descent varies from country to country. In the USA, some transfusion services screen donors for sickle cell trait, as recommended by the Association for the Advancement of Blood and Biotherapies,[37] to ensure that people with sickle cell disease do not receive blood containing HbS. In France, there is no screening for sickle cell trait in donors, and patients could, therefore, receive red blood cells containing HbS, albeit at a lower frequency than in LICs, due to the much smaller proportion of donors of African descent, and the frequency of leukodepletion failure associated with the sickle cell trait. Some bioactive substances are released into donated blood during storage, whereas other bioactive substances are already present in large amounts in fresh blood products.[38] Longer storage times have been shown to be associated with increased rates of alloimmunisation in mice.[39] One study reported that red blood cell antibody formation in people with sickle cell disease was significantly associated with the use of older age red blood cells (>35 days) at the time of transfusion.[40] This finding has not been substantiated by other studies on people with sickle cell disease.[22,41] Due to the scarce availability of blood donations in Africa and the frequent use of blood from replacement donors (ie, donors who are relatives of the patient and who donate blood to meet the needs of the patient), storage time of donated blood is often short. For this reason, practices are moving towards the provision of red blood cell concentrates.[8] In HICs, where the donor population is predominantly of European descent, the turnaround time for red blood cell units can be short. This short turnaround is the case in France where the need for prophylactic red blood cells matching for ABO, RhD, C, c, E, e and K is growing but the pool of donors of African descent is not increasing in parallel. It is particularly problematic when extended matching protocols for Fy, Jk, and MNS are applied for patients who develop antibodies. Given the scarcity of donors of African descent in France, it is challenging to transfuse red blood cells matched for C and c and E and e, and about 40% of the red blood cell concentrates transfused to patients with sickle cell disease with a D+C−E− phenotype are obtained from donors of European ancestry who have a D−C−E− phenotype.

One important difference between HICs and LICs is leukodepletion, which is implemented in almost all HICs. Leukodepletion reduces HLA immunisation,[42] but conflicting results have been obtained concerning its effects on red blood cell alloimmunisation. Few data are currently available, but one retrospective study, including patients with various underlying diseases, reported that pre-storage leukodepletion did not reduce the rate of red blood cell alloimmunisation, whereas another study on people with sickle cell disease reported reduced rates of alloimmunisation following transfusion with leukoreduced blood.[14,43] However, leukodepletion has been reported to attenuate the proinflammatory properties of storage-derived microvesicles, potentially affecting inflammation-driven alloimmunisation.[44] It is not known whether white blood cells constitute an important additional risk factor for red blood cell alloimmunisation in LICs.

The immunogenetic background of people with sickle cell disease

Although some people develop antibodies very quickly from transfusion, others, despite the previously outlined factors, never become immunised. This observation has prompted many studies on the immunogenetic factors associated with responder or non-responder status. HLA has been widely studied in this context. In the general population and in people with sickle cell disease, DRB1 molecules have been shown to be associated with the response to specific antigens or with a more global responder or non-responder status.[45–49] Other genetic factors, such as polymorphisms of Fc gamma receptor genes have been associated with the responder status of people with sickle cell disease.[50–52] Routinely predicting whether a patient will respond to a certain red blood cell antigen on the basis of identified genetic factors and considering specific prevention strategies aimed at those at high risk of developing antibodies is unrealistic at the moment.

Similarly, the phenotype and functionality of immune cells (ie, T cells, B cells, and subtypes) have been studied in polytransfused patients with sickle cell disease, revealing differences between responders and non-responders.[53–55] However, given the difficulties involved in setting up prospective studies to monitor alloimmunisation events in real time, no such study has ever been performed to identify a particular immune status that is likely to promote alloimmunisation to specific antigens before the first transfusion event has occurred in a patient. Studies in mice that have focused on different immune conditions or studies with different antigen models, have greatly increased our understanding of the mechanisms of alloimmunisation, but these studies have not yet lead to any practical applications in patients with sickle cell disease.[56,57] However, experience with other antibody-mediated and complement-mediated diseases has led to the use of some drugs, such as rituximab (an anti-CD20 antibody) in immunised patients with a history of severe haemolytic transfusion reactions.[58] Although, no additional antibodies develop in patients treated with rituximab,[58] some patients might encounter mild post-transfusion haemolysis without detectable antibodies, revealing the complexity of the pathophysiology of this syndrome in sickle cell disease. Eculizumab (an anti-C5 convertase antibody),[59,60] is another example of a new drug being implemented, and as of 2022, so is tocilizumab; however, tocilizumab is only used to treat severe haemolytic transfusion reactions.[27]

Challenges to improve prevention of alloimmunisation in HICs and LICs

Improvements are still clearly required in both LICs and HICs, with each of the factors presented in this Viewpoint having a different effect in the prevention of alloimmunisation (figure 2).

Challenges in HICs

In HICs, given the high rates of alloimmunisation, its prevention in people with sickle cell disease remains a real challenge. The risk of alloimmunisation and subsequent haemolytic transfusion reactions is currently estimated for each patient on the basis of the indication for transfusion (acute event *vs* chronic transfusion programme) and the capacity of the patient to respond to many different foreign red blood cell antigens, which can only be assessed on the basis of previous alloimmunisation.[22,29,41] The preventive measures currently proposed range from matching for ABO, RhD, C, c, E, e, and K only to extended matching for Fy^a, Fy^b, Jk^a, Jk^b, S, and s in alloimmunised patients. Rituximab could be considered if patients have a history of severe post-transfusion haemolysis due to alloimmunisation.[61]

Based on current practices, a first consideration is judicious indications of transfusion. The indications for occasional transfusion in acute, inflammatory situations should be weighed up against the risk of immunisation and of developing post-transfusion haemolysis, particularly in patients with history of alloimmunisation at high risk of developing additional antibodies.[29,41] Some indications for transfusion, such as cholecystectomy, have already been re-evaluated and restricted, with no vaso-occlusive consequences.[62]

Efforts should be made to increase the availability of red blood cell units with blood group phenotypes closely matching those of the recipients. Increasing availability is a major challenge that will require promoting blood donation within populations of African descent in HICs. A precise knowledge of transfusion history is also required but is not always available in HICs without a centralised information system. The maintenance of a well kept transfusion file accessible to all hospitals is an important objective.

In matching strategies, genotyping is also an issue, both in patients and donors, particularly for extended deduced phenotypes in the Fy, Jk, and MNS blood groups, for minor antigens, for which antiserum samples are not available. Genotyping is also required for accurate characterisation of Rh variants in patients. However, the benefits, cost, and feasibility of generalising Rh variant-matching strategies remain unclear and prospective investigations are required, particularly given the very large number of variants, of different clinical and biological significance in the transfusion context.[9] The same considerations arise for the detection of antibodies developed against red blood cell antigens typically found in people of African descent and considered as low-frequency antigens in populations of European descent in HICs (figure 1). These antibodies can develop in patients receiving blood from donors of African descent. They could be detected with specific red blood cell test panels carrying low-frequency antigens. Prospective studies will be required to assess

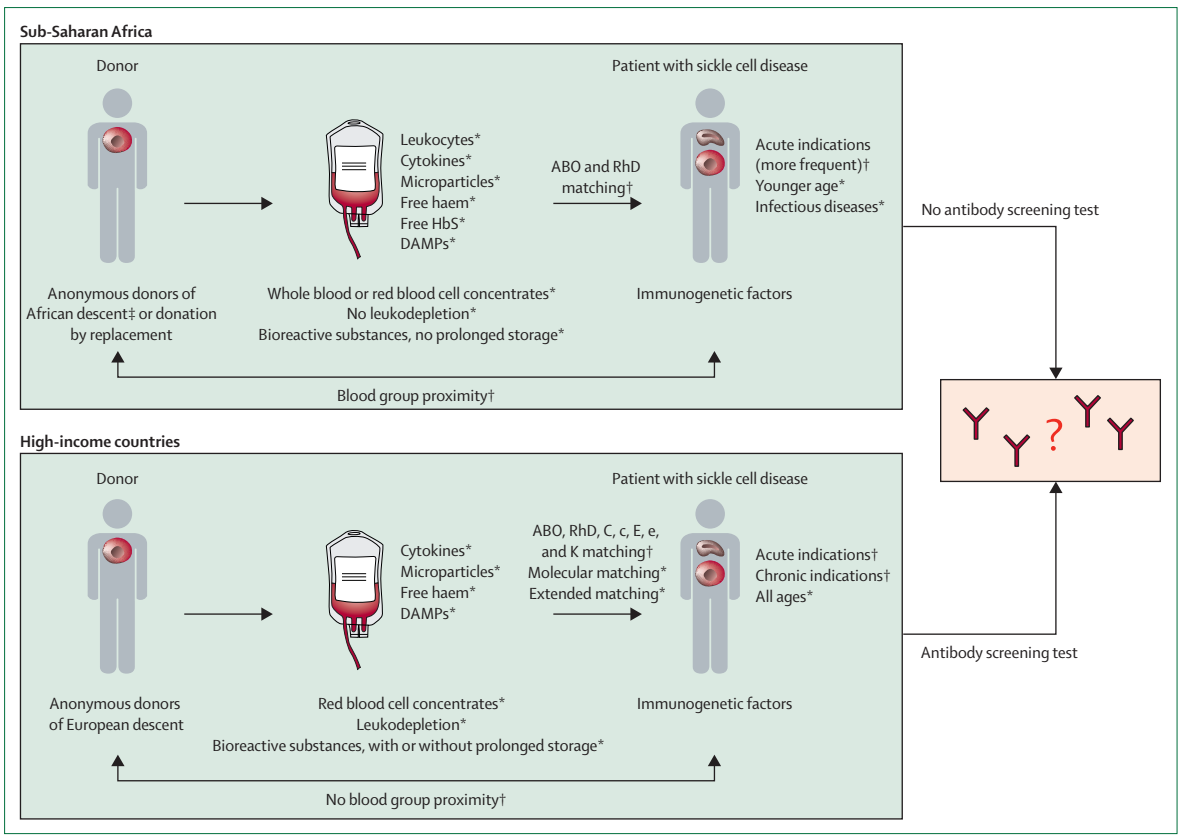

Figure 2: **Risk factors for alloimmunisation in high-income countries and sub-Saharan African countries**
DAMPs=damage-associated molecular patterns. HbS=sickle cell form of haemoglobin. *Risks for which additional investigations are required (shown only in animal or in-vitro studies, or are hypothetical). †Risks and measures that have strong scientific evidence. ‡G6PD deficiency occurs in approximately 10% of donors of African descent.

the benefit–risk ratio, bioclinical significance, and cost of such a strategy. Finally, the introduction of immunosuppressive treatments to prevent alloimmunisation targeting B cells or plasma cells should be formally evaluated. The American Society of Hematology guidelines consider the use of rituximab as a conditional recommendation based on the very low certainty of the evidence to support its benefit.[7] Many other candidate drugs that target plasma cells could be explored with, for example, drugs potentially able to decrease inflammation.

In HICs, in addition to improving current practices, many areas of investigation remain open. The identification of patients likely to be high responders to red blood cell antigens and develop a reaction at first presentation is a major issue, as such identification would make it possible to improve patient stratification and set preventive measures.

As for recipient status, there is currently little evidence concerning the modulation of alloimmunisation by blood product content, manufacturing, and storage. These data could drive the development of novel bench-to-bedside applications to prevent alloimmunisaton. Prospective studies assessing the effect on alloimmunisation of the bioactive substances transfused into patients are now required. These studies will make it possible to optimise manufacturing processes and storage for red blood cell concentrates for people with sickle cell disease, and to determine whether it is necessary to exclude blood donations from individuals with sickle cell trait or G6PD deficiency.

Alloimmunisation results from interactions between the donor, product, and recipient status at a given time.[57] Investigations of all these aspects would, therefore, make it possible to implement personalised transfusion medicine for people with sickle cell disease, with a preventive patient stratification strategy based on matching, blood product characteristics, and the use of additional prophylactic drugs.

Challenges in LICs

In LICs, particularly in sub-Saharan Africa, the first major challenge will be upgrading the blood group matching strategy. Prophylactic matching for ABO, RhD, C, c, E, e, and K would greatly decrease alloimmunisation rates compared with matching only for ABO and RhD. Many studies have shown the efficacy of this measure in the USA, Europe, and some Middle Eastern countries,

Search strategy and selection criteria

We identified references for this Viewpoint manuscript by searching PubMed on Feb, 1, 2023, for articles published between Jan 1, 2010, and Feb 1, 2023, with the search terms "blood transfusion", "Sickle cell disease", "red blood cell alloimmunization" "risk factors" "storage" "immunomodulation", alone and in combination with "sub-Saharan Africa", exclusively in English. The final reference list was generated on the basis of relevance to the broad scope of this Viewpoint, with few studies from before Jan 1, 2010 considered because they are seminal in this field.

in which alloimmunisation rates are also high in people with sickle cell disease.[7,63–65]

Another major challenge facing LICs is the improvement of immuno-haematological follow-up, as patients do not generally undergo antibody-screening tests to detect alloimmunisation or to determine the specificity of antibodies. The feasibility of such measures is limited by the ability to phenotype donors and recipients, and to perform pre-transfusion and post-transfusion analysis, which can be costly.

The first step towards developing strategies to improve the immunological safety of transfusion for people with sickle cell disease in sub-Saharan Africa and to persuade decision makers to invest funds in this field, would be an evaluation of the real burden of the consequences of alloimmunisation. All the studies done in sub-Saharan Africa have reported on allo-immunisation rates, but none has focused on the consequences of alloimmunisation, such as increase in transfusion needs or the effect on disease severity for those who develop haemolytic transfusion reactions, leading to an overall increase in the cost of managing the disease. Collaborations with HICs could be established to investigate these matters.

Whole blood is the principal type of blood product used in LICs, and the effect of the absence of leukodepletion on alloimmunisation should be considered. In the scale of priorities, however, this goal is probably not the most essential as the cost of leukodepletion is high and there is a scarcity of strong evidence concerning its effect on red blood cell alloimmunisation.

Conclusion

LICs and HICs must learn from each other to ensure benefit to patients through the implementation of transfusion strategies preventing alloimmunisation while remaining mindful of the benefit–cost ratio and resource availability in LICs. If we are to reach the goal of personalised transfusion medicine in different environments and with different practices, HICs and LICs must work together to address the issues raised in this Viewpoint—eg, the effect on alloimmunisation of the sickle cell trait and G6PD genetic characteristics of donors of African descent, and the clinical effect of Rh variants and specific red blood cell antigens (ie, low-frequency antigens) typically found in people of African descent. However, while prevention of alloimmunisation in both HICs and LICs might decrease the rate of haemolytic transfusion reactions, it is not sufficient to resolve this problem, as there are many described haemolytic transfusion reaction cases of unexplained pathophysiology in patients without detectable antibodies.[2,66]

Contributors

All authors conceptualised the manuscript. FP wrote the original draft of the manuscript and performed the review of the litterature. AF and SD edited the manuscript and approved the final version for submission.

Declaration of interests

We declare no competing interests.

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