Hemolytic transfusion reactions in sickle cell disease: underappreciated and potentially fatal

Ferrata Storti Foundation

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Haematologica 2020
Volume 105(3):539-544

Introduction

Patients with sickle cell disease (SCD) often receive red blood cell (RBC) transfusion support for the prevention and management of many acute and chronic disease complications.[1-3] The beneficial effects of transfusion therapy observed in recent clinical studies, and the lack of effective treatments for this population of patients, have led to an increased use of blood.[4] While RBC transfusions may be life-saving, we are concerned about their expanding use and would like to raise awareness of RBC alloimmunization, a major complication of transfusion, particularly in patients with SCD in whom the incidence is much higher than in other groups of patients.[5] Hemolytic transfusion reactions, which primarily occur in RBC alloimmunized patients, are often under-recognized in patients with SCD, in particular because the symptoms mimic those of acute vaso-occlusive crises, and serological markers of new alloantibodies may be equivocal.[6,7] In addition to increasing the risk of potentially fatal acute or delayed-type hemolytic transfusion reactions (DHTR),[8-10] the development of RBC alloantibodies can also significantly delay the procurement of compatible RBC for future transfusions.[11]

Currently, there is a lack of evidence in this area to inform best practice, and management is often based on anecdotal case reports. While there have been reports of a variety of cases illustrating the challenges associated with recognizing and treating hemolytic transfusion reactions in patients with SCD,[12,13] the potential reasons for the higher incidence of RBC alloantibodies in SCD patients merit discussion. Here, we share our experience in managing alloimmunized patients and hemolytic transfusion reactions, and challenge the medical community to consider lessons learned from diagnostic criteria and mitigation policies for transfusion-related acute lung injury (TRALI) in order to minimize the morbidity and mortality associated with transfusion in patients with SCD.

Why are patients with sickle cell disease at high risk of red blood cell alloimmunization?

One possible reason for the relatively high incidence of alloimmunization observed in patients with SCD is the mismatch in RBC antigens expressed in the donor pool (primarily Northern European descent) and patients with SCD (mainly of African descent).[8] Mismatch of RBC antigens is not the only reason, however, as a significant proportion of patients with SCD who receive phenotypically matched blood from exclusively ethnically matched donors still become alloimmunized.[9] Molecular analyses of the *RH* genes in patients with SCD and African-American donors reveal remarkable *RH* allelic diversity in this population, with mismatch between serological Rh phenotype and *RHD* or *RHCE* genotype due to variant *RH* alleles in a large proportion of the individuals.[10] Thus, *RH* genotyping in addition to serological typing may be required to identify the most compatible RBC, though it is not yet known if such an approach completed prospectively instead of reactively (after antibodies against alloantigens in the *RH* family form) will decrease RBC alloimmunization, and whether it will be possible to source rarer *RH* genotypes on a regular basis for patients on a transfusion program. The clinical context of RBC transfusion in SCD may also contribute to the higher rate of alloimmunization; the

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Received: August 26, 2019.
Accepted: December 18, 2019.
Pre-published: February 6, 2020.

doi:10.3324/haematol.2019.224709

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/105/3/539

risk of alloimmunization in SCD is increased when patients are transfused for acute complications, such as acute chest syndrome, acute pain and acute multi-system organ failure, which are clinical complications marked by significant inflammation. Thus, unique aspects of transfusion therapy in patients with SCD, in conjunction with other possible immune perturbations, appear to place such patients at a particular risk of RBC alloimmunization.[5,14-17]

Definitions of acute and delayed hemolytic transfusion reactions and hyperhemolysis

While acute hemolytic transfusion reactions can largely be avoided by stringent alloantibody investigations prior to transfusion, DHTR, which typically occur days or weeks following the implicated transfusion episode of seemingly compatible RBC,[7] are more difficult to avoid. The delayed nature of DHTR is thought to reflect the recrudescence of an alloantibody not detected at the time of the RBC compatibility testing just prior to transfusion.[6,18,19] The inability to detect RBC alloantibodies at the time of transfusion presumably reflects evanescence of a prior alloantibody response to a level below the detection threshold in routine clinical assays. Following re-exposure to the implicated alloantigen, immunological memory generated during the primary encounter facilitates an amnestic immune response that results in the rapid production of alloantibodies against the transfused unit (Figure 1). This in turn causes destruction of the transfused RBC, which is often accompanied by clinical symptoms associated with accelerated hemolysis.[18,19] DHTR

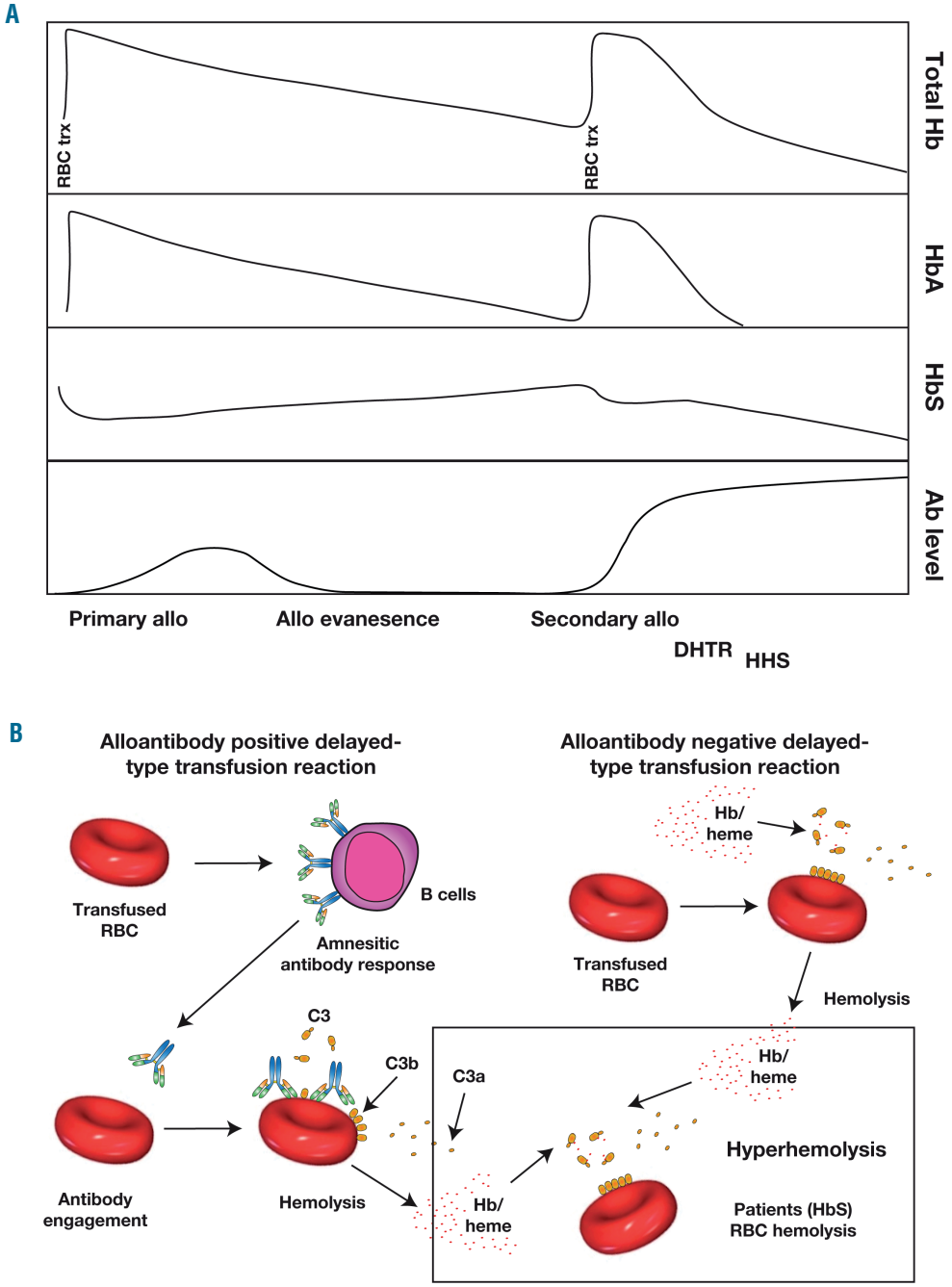

Figure 1. Delayed-type hemolytic transfusion reactions. (A) Exposure to a red blood cell (RBC) alloantigen through transfusion or pregnancy can result in the development of alloantibodies (allo) that quickly evanescence over time, possibly preventing their detection prior to a subsequent transfusion. Re-exposure to RBC expressing the same alloantigen can induce an amnestic alloantibody response, which can cause accelerated clearance of the transfused RBC, resulting in hemolysis and a delayed-type transfusion reaction (DHTR). Alloantibody-induced clearance of transfused RBC can occasionally result in hyperhemolysis, otherwise known as hyperhemolytic syndrome (HHS), which is signified by the accelerated clearance of the patient's own RBC and which can be particularly fatal. (B). Alloantibodies that develop in response to exposure to alloantigens can lead to direct clearance of RBC through a variety of antibody effector mechanisms, including complement activation. Sometimes patients will experience a DHTR in the absence of a detectable alloantibody; an alloantibody may be present and simply be below the detection threshold of clinical assays or an alloantibody may be absent entirely, with the DHTR possibly reflecting heme-mediated complement activation and RBC hemolysis. Regardless of the mode of hemolysis experienced by transfused RBC in the setting of a DHTR, heme released may activate complement, thereby potentially contributing to the development of hyperhemolysis. Trx: transfusion; Hb: hemoglobin.

can be further complicated by bystander hemolysis or hyperhemolysis, a process that results in the accelerated clearance of both the transfused RBC and the patient's own RBC[20,21] (Figure 1). Such hyperhemolysis can be particularly fatal in patients with SCD for reasons that remain incompletely understood.

Attention to a high incidence of delayed hemolytic transfusion reactions

While DHTR can be life-threatening, unawareness of their frequency and lack of severity of these transfusion reactions have likely resulted in too little attention regarding their potential impact on overall SCD morbidity and mortality. For years, the overall incidence of DHTR per transfusion in SCD was estimated to be around 1:1000.[22-24] making it a relatively uncommon transfusion reaction in this population of patients. However, newer reports suggest that these data may be misleading. As mentioned previously, given the similarities between the clinical presentation of DHTR and the more common complications of vaso-occlusive crises, DHTR can be easily missed.[6,7,25] Unless an alloantibody screen is performed, an amnestic alloantibody response will not be detected and a diagnosis of DHTR may not be entertained. Furthermore, as some reports suggest that as many as 30% of DHTR can be alloantibody-negative,[14,26] clinicians must rely on HbA measurements obtained within 48 h of the implicated transfusion and at the time of a presumptive DHTR in order to make a reliable diagnosis of DHTR[12,27] (Figure 1). Unfortunately, alloantibody screens and HbA values are not routinely ordered following transfusion or in recently transfused patients admitted for acute pain, raising the possibility that the incidence of DHTR in patients with SCD may be much higher than previously appreciated.[27]

In an effort to assess the incidence of DHTR more accurately, a recent prospective study evaluated adult patients after transfusion using total Hb, HbA and HbS quantification within 48 h after all transfusions and defined DHTR as a significant decrease in HbA (>50%) and/or in total Hb levels (>30%) within 25 days of a trigger transfusion along with hemoglobinuria, symptoms of a vaso-occlusive crisis, and/or worsening symptoms of anemia.[27] Using this approach, a DHTR was found to occur following 4.2% of episodic transfusions,[27] over ten times more frequently than previously speculated, making DHTR the single most common adverse event following episodic transfusion in patients with SCD. Nearly 11% of all patients with DHTR died,[27] suggesting that these reactions are not only more common than previously suggested, but also likely to affect SCD mortality significantly. These results provide one possible explanation for the recent observation that alloimmunized patients with SCD have a much higher mortality rate than non-alloimmunized individuals with SCD.[28]

Comparison of delayed hemolytic transfusion reactions with transfusion-related acute lung injury

There are resemblances between the underappreciated incidence and impact of DHTR in patients with SCD and the history of other transfusion reactions with fatal outcomes.[29] Until relatively recently, TRALI was a rarely recognized complication of primarily platelet and plasma transfusion defined by acute lung injury within 6 h of transfusion in the presence of hypoxia, with radiographic evidence of bilateral infiltrates in the absence of circulatory overload.[30] Because patients who are susceptible to TRALI often have significant comorbidities, changes in pulmonary function that accompanied transfusion were historically attributed to other etiologies.[31] However, once the impact of TRALI was recognized and regulatory agencies heightened hemovigilance efforts, TRALI quickly became identified as the most common cause of transfusion-related mortality in the USA and Europe.[32] Epidemiological studies found associations between blood products donated from multiparous women and other donor factors that increased the likelihood that a recipient would develop TRALI.[32] In particular, anti-HLA and other anti-leukocyte alloantibodies that may bind and activate leukocytes intravascularly became implicated in the pathogenesis of TRALI.[33-35] Implementation of manufacturing practices that excluded multiparous females and other donors who appeared to increase the risk of TRALI in transfusion recipients has resulted in a significant reduction in TRALI cases.[36,37] Thus, TRALI provides a key example of an underappreciated transfusion complication that can result in significant morbidity and mortality and that, upon additional study, improved diagnostic criteria and changes in clinical practice, has dramatically reduced in incidence over time.[31]

Strategies to prevent delayed hemolytic transfusion reactions

The most effective way to prevent a DTHR is to avoid unnecessary RBC transfusion. When transfusion avoidance is not feasible, provision of the most compatible RBC units is recommended. In an effort to reduce the risk of DHTR, transfusion services keep records of previously identified alloantibodies in order to reduce the risk of re-exposure to a particular alloantigen once an alloantibody has been detected. Using this approach, hospital transfusion services provide RBC that are negative for the particular alloantigens against which a patient has previously made alloantibodies. However, when patients seek care in multiple healthcare systems this information is often not available.[38,39] In this setting, transfusion services can only rely on transfusion histories at the presenting facility or other facilities if obtainable, which are often either not obtained or incomplete.[38,39] As this approach often results in inadequate alloimmunization histories,[40] multiple encounters in different healthcare systems place patients with SCD at a significantly high risk of DHTR.[38] Furthermore, transfusions are often initiated when patients present with acute complications at centers where providers may not be familiar with SCD management, including transfusion complications. Implementation of healthcare-wide acute care plans for patients with SCD that include consideration of possible transfusion complications may provide the type of guidance needed to increase awareness among all providers within a healthcare system.

Nonetheless, despite effective communication between healthcare systems, alloantibodies may not be detected if antibody evaluations are not routinely completed following transfusion episodes that are at a higher risk of inducing alloantibodies. This reflects the ability of newly formed alloantibodies to fall below the level of detection prior to a subsequent transfusion evaluation, which may occur months to years later.[41] Thus, RBC alloantibody evanescence can contribute significantly to the risk of DHTR in the absence of systematic post-transfusion sero-

logical evaluation. To avoid these challenges, routine serological testing should be considered for all SCD patients 1 to 3 months after each transfusion episode.[42] Even with such a policy in place, up to 30% of DHTR with bystander hemolysis occur in the absence of any detectable alloantibody,[14,26] making it particularly difficult to predict and prevent these transfusion reactions fully.

Shared laboratory data between hospital systems is critical

Significant barriers to laboratory information exchange exist in many healthcare systems in many countries, and efforts that allow alloantibody identification histories of all patients (including those with SCD) to be shared between such systems must become a priority. This critical patient safety initiative would facilitate antibody identification in a patient's sample, would decrease the burden of identifying optimal RBC units when working with incomplete transfusion histories, would increase the timely provision of fully compatible RBC units, and would decrease the incidence of DHTR.[38,39] Currently, the lack of such data sharing prevents many transfusion services from knowing the transfusion requirements of newly encountered patients with SCD at the time of a transfusion request,[40] or from knowing the availability of compatible RBC once alloantibodies have been characterized.[11,43] If complex alloantibody profiles were known *a priori* and corresponding donor databases were available, compatible donor units could be readily identified, allowing transfusion requirements to be addressed in a more timely and safe manner.[38,39,44]

Routine post-transfusion antibody screening and HbA quantification should be considered to improve identification of red blood cell alloantibodies and delayed hemolytic transfusion reactions

Although additional studies are certainly needed to establish the incidence of DHTR in various hospital settings, more uniform detection of these reactions is important if future DHTR are to be avoided and if effective treatment strategies are to be implemented.[45] While patients may experience accelerated clearance of transfused RBC in the absence of clinical systems, to facilitate detection of clinically meaningful DHTR, we recommend that patients with SCD with a history of transfusion in the preceding 21 days who present with any complication requiring medical attention should be evaluated with an antibody screen regardless of whether or not another RBC transfusion is warranted. Using this approach, a higher percentage of alloantibodies that form as a result of a recent transfusion should be identified. However, as nearly 30% of DHTR have been reported to occur in the absence of detectable alloantibodies,[14,26] evaluation for DHTR will also require acquisition of HbA values following transfusion and at the time of clinical presentation of any complication requiring medical attention.[27] As episodic transfusions are much more likely to be initiated during acute complications and result in DHTR,[6,7,27] polices that include obtaining HbA values within 48 h following an episodic transfusion may be particularly helpful when interpreting a HbA value at the time of suspected DHTR. Thus, we recommend considering routine HbA measurements following any episodic RBC transfusion and an antibody screen and HbA measurement at the time of any hospital presentation within 21 days of the most recent episodic transfusion (Table 1).

Therapeutic options for ongoing delayed hemolytic transfusion reactions

In addition to facilitating more accurate diagnoses of DHTR, routine approaches aimed at identifying DHTR will allow consideration of more effective therapeutic options for ongoing DTHR; these therapies are particularly important to consider for DHTR involving hyperhemolysis. Erythropoietin and intravenous iron are often given to boost endogenous RBC production in a setting of severe anemia.[12] Plasmapheresis has also been attempted

Table 1. Recommendations for better prevention, more accurate diagnosis and improved treatment of delayed-type hemolytic transfusion reactions in sickle cell disease.

Prevention:
National and International
1) RBC alloimmunization databases
2) RBC donor databases
Institutional
1) Reduce RBC alloimmunization through prophylactic matching for Rh (C/c, E/e) and K antigens.
2) Judicious use of RBC transfusions
3) Routine alloantibody evaluation for all patients with SCD within 1 to 3 months after each episodic transfusion (while rare, some alloantibodies may not be detectable within 3 months after transfusion)
Diagnosis:
Institutional
1) Alloantibody screen for any SCD exacerbation within 21 days of transfusion (regardless of whether another transfusion is being considered)
2) HbA quantification within 48 h following episodic transfusion and at the time of any SCD exacerbation occurring within 21 days of a transfusion
***Treatment*:**
Institutional
1) Supportive care (including erythropoietin and iron)
2) Intravenous immunoglobin and corticosteroids
3) Consideration of treatment with complement inhibitors in cases of severe DHTR (including those with hyperhemolysis)
4) Consider rituximab prophylaxis in cases with a history of severe DHTR and only "least incompatible" blood can be sourced for transfusion.

RBC: red blood cell; SCD: sickle cell disease; HbA: hemoglobin A.

to reduce heme levels,[46] although the level of anemia and inability to transfuse may prevent this from becoming a realistic option in many patients. Intravenous immunoglobulin and corticosteroids may further reduce hemolysis in the setting of DHTR.[47] While characteristics of the transfused unit, such as RBC storage, may have an impact on transfusion outcomes in SCD,[48] recent studies suggest that exuberant complement activation may account for the most severe DHTR with accompanying hyperhemolysis.[49] Consistent with this, treatment of patients experiencing DHTR-associated hyperhemolysis with eculizumab, an anti-C5 complement-blocking antibody, has been shown to reverse complement activation, reduce hemolysis, and result in rapid clinical improvement.[49,50] While additional studies are needed, these reports hold promise and suggest that more effective treatment options that could significantly improve patients' care may be on the horizon (Table 1).

Avoiding additional RBC transfusion at the time of an ongoing DHTR with bystander hemolysis is recommended, as transfusion of even seemingly compatible RBC that are negative for all alloantigens that the patient is known to be alloimmunized against may worsen the ongoing hemolysis. If the alloantibody in question cannot be identified or if it is identified but compatible units cannot be allocated, alloantibody function tests can be ordered to assess the clinical significance of a patient's alloantibodies. This test typically involves evaluation of monocyte engulfment of antibody-coated cells *in vitro* as a read out of alloantibody function.[51] However, this approach is time-consuming, and may not provide timely results in an acute setting.[51] Should the clinical status of the patient necessitate consideration of a "least incompatible" RBC transfusion, rituximab prophylaxis has been described to reduce DHTR in small case reports.[52,53]

Summary

In conclusion, RBC alloantibodies and DHTR are not uncommon in patients with SCD. They are underappreciated and, in our opinion, are the single leading cause of transfusion-associated morbidity and mortality in this vulnerable population of patients. Many of the challenges associated with preventing and treating DTHR can be addressed by developing international and national RBC alloantibody databases, limiting RBC transfusions to situations that are evidence-based, implementing more accurate diagnostic strategies (through routine use of HbA quantification and standard antibody screening), better understanding the pathophysiology, and formally testing additional prophylactic and treatment approaches to prevent and treat these reactions. We urge our colleagues in hematology, transfusion medicine (from donor centers to transfusion services), laboratory information technology, funding agencies, and regulatory agencies to view RBC alloimmunization and DTHR in patients with SCD with a similar urgency as TRALI was viewed in past decades. Such a heightened awareness, and subsequent industry changes, are predicted to directly reduce the significant transfusion-associated complications that contribute to the current morbidity and mortality of patients with SCD.

Acknowledgments

This perspective was initially conceived as a result of a post-conference formal meeting after the first international conference on delayed type transfusion reactions in Creteil, France. We thank all those who organized, supported and attended this conference, while particularly acknowledging those who directly participated in the post meeting and subsequent discussions on this topic, including Karina Yazdanbakhsh, Armand Mekontso Dessap, Lubka Roumenina, Eldad Hod and Chris Tormey.

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