Received: 27 November 2020 | Revised: 11 July 2021 | Accepted: 16 July 2021

DOI: 10.1111/trf.16640

REVIEW

TRANSFUSION

The transfusion management of beta thalassemia in the United States

CME/SAM

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Funding information
U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Grant/Award Number: 1 NU58DD000002-01-00; U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, Grant/Award Number: U1AMC28548

1 | INTRODUCTION

The β thalassemia syndromes constitute the most frequent inherited anemia managed with chronic red cell transfusions around the world.[1,2] The prevalence of thalassemia in the United States was underestimated in past surveys that were limited only to the major specialty centers.[3] Recent data show that the aggregate number of patients followed at smaller centers and community practices surpasses those at the major centers.[4] A precise estimate of the total number of individuals with thalassemia in the U.S. is unavailable due to the lack of either a state or national database. Surveys have shown that 10 large thalassemia centers in the country collectively follow about 1100 patients, while additional 1500 patients are estimated to receive care at other hospitals.[4,5] The Thalassemia Western Consortium (TWC) study showed that of the 717 patients, 44% of patients had β thalassemia syndromes (including 15% with HbE β thalassemia) and 55% had various α thalassemia disorders. Transfusion-dependent patients comprised 35% of the population, 9% had received 1 or more life-time transfusions, and 56% had never been transfused. Thus,

Abbreviations: NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia; TWC, Thalassemia Western Consortium.

characterization of the patients reveals a diverse population consisting of multiple ethnic groups due to trends in immigration that have a wide mix of pathogenic mutations and heterogeneity of disease expression.[4,6–8] This introduces a unique challenge to developing a standardized approach to transfusion therapy for thalassemia in the U.S.

The TWC is an alliance of 10 academic hematology centers in the Western region (located in California, Washington, Oregon, Nevada, and Arizona) that is supported with federal project funds to study the transfusion practices and complications in thalassemia.[4] Previous data from TWC showed that important differences exist in the approach to transfusions for various types of thalassemia, targets for pre-transfusion hemoglobin level, processing of red cell units, degree of phenotypic matching, and the management of red cell alloimmunization.[4,9] The Consortium recognized the need for evidence-based recommendations for transfusions in thalassemia. However, there is a lack of clinical trials that consider the advances in supportive care in the past two decades, such as the introduction of oral iron chelators and the decline of splenectomy. In the absence of directly relevant research, the existing transfusion guidelines for thalassemia were developed by expert panels.[10,11]

We convened a multi-disciplinary committee consisting of pediatric and adult hematologists and transfusion medicine specialists to develop recommendations for the transfusion management of β thalassemia (Appendix S1). The α thalassemia disorders, which include deletional and non-deletional forms of hemoglobin H disease and α thalassemia major (Hb Bart hydrops fetalis), have several unique genetic and clinical aspects[7,8,12] that should be addressed by a separate set of recommendations for management. Here, we discuss the rationale for transfusion therapy in β thalassemia, the challenges in developing transfusion recommendations, and the sources and limitations of existing guidelines for the U.S. patient population. The transfusion recommendations are the unified opinion of the Consortium based on the multidisciplinary principles of optimizing patient outcome and satisfaction, reducing transfusion complications, and facilitating blood inventory management. These are the first recommendations directed toward hematologists and transfusion medicine specialists that are designed to specifically address concerns that are pertinent to the thalassemia population in the U.S.

2 | THE ROLE OF RED BLOOD CELL TRANSFUSIONS IN THALASSEMIA

2.1 | Management of anemia

Beta thalassemia is caused by β-globin gene (*HBB*) mutations that reduce synthesis of normal adult hemoglobin molecule (HbA).[13] The severity of the resulting anemia and the need for transfusion support are influenced by the nature of the β-globin mutations, compensation by fetal hemoglobin, and the imbalance between α- and non-α-globin chains.[13,14] The primary management of severe anemia in β thalassemia is the provision of adequate red cell transfusions.[15–17]

Chronic anemia has serious consequences for individuals with thalassemia. In children, low hemoglobin levels are associated with reduced physical activity, impaired growth, enlargement of liver and spleen, osteopenia, delayed puberty, and cognitive impairment.[17–20] In adults, chronic fatigue, reduced work capacity, cognitive impairment, osteopenia and fractures, hypersplenism, and reduced quality of life are observed.[21–25]

2.2 | Control of ineffective erythropoiesis

Ineffective erythropoiesis is a distinctive and principal characteristic of β thalassemia, leading to anemia and massive bone marrow hyperplasia.[13,20,26,27] As α-globin chains aggregate in developing red blood cells due to β-globin deficiency, 60%–80% of progenitors die at the polychromatophilic stage.[28–31] The erythropoietin-driven expansion of erythroid precursors and shortened red cell survival causes hepatosplenomegaly, elevated basal metabolism, extra-medullary hematopoietic masses, skeletal deformities of face and skull, and fragile bones.[20,32–35] Concurrently, the suppressed production of hepcidin increases dietary iron absorption and releases iron from body stores.[36,37] The hemoglobin threshold to suppress ineffective erythropoiesis may be higher than the level needed to alleviate symptoms of anemia.[37,38]

2.3 | Improving oxygen transport

Mutations affecting the β-globin gene which lead to either an absence of β-globin chain production (β^0 thalassemia) or a variable reduction in their output (β^+ thalassemia) eventually result in anemia as well as abnormal hemoglobin composition.[39] HbA is reduced or absent in β thalassemia, accompanied by a variable increase in the absolute amount and proportion of HbF.[40] The predominance of HbF with high oxygen affinity in the red cells makes oxygen delivery less efficient.[13,23,41] Compared with the other transfusion-dependent anemias, individuals with thalassemia can become symptomatic with fatigue at a higher hemoglobin level and display an increase in bone marrow activity. Individual differences in adaptation to anemia are

due to variability in hemoglobin composition and other unknown factors.[41–43] This is particularly noted in HbE β thalassemia where HbE has normal oxygen affinity similar to HbA and contributes toward an improved tolerance to anemia.[41,44]

3 | CHALLENGES IN DEVELOPING TRANSFUSION RECOMMENDATIONS FOR THALASSEMIA

The focus of contemporary management of thalassemia is health-related quality of life throughout the lifespan. Where studies on transfusion therapy in children have addressed key clinical endpoints (growth delay, skeletal changes, and splenomegaly), the adult studies have examined pathophysiological markers (reductions in blood volume, erythroid mass, and plasma iron turnover). Transfusion practices during childhood may impact the prevalence of bone disease and chronic pain in the aging adult patients.[45] It is also likely that extending chronic transfusions to many patients with thalassemia intermedia will lead to better long-term quality of life.[22,23] However, it is not be feasible to address these critical questions through short-term clinical trials. Apart from these considerations, creating transfusion guidelines for thalassemia is impeded by other challenges.

3.1 | Distinct transfusion thresholds and goals in thalassemia compared with other transfusion-dependent anemias

Many factors, some poorly understood, influence individual response to anemia apart from the hemoglobin level.[46,47] This introduces complexity in developing standard or uniform transfusion guidelines for all thalassemia syndromes. The 2016 AABB Red Blood Cell Guidelines[48] recommending a hemoglobin threshold of 7–8 g/dl specifically do not apply to chronic transfusion-dependent anemias such as thalassemia.

Red cell transfusions can sustain normal physical appearance, growth, and activity in children with thalassemia through the reversal of anemia and marrow hyperplasia.[49] Likewise, adults can achieve normal functioning in the professional and personal spheres.[50,51] These are the benchmarks to judge the success of transfusion therapy in thalassemia today. However, even among the contemporary cohort of individuals with thalassemia, many are unable to receive transfusions that enable this goal.

3.2 | Under-utilization of blood transfusions in thalassemia

Improper targets for hemoglobin in thalassemia can lead to persistence of symptomatic anemia and bone marrow hyperplasia.[38,52] Over-transfusion is also a risk, but this appears to be much less common based upon clinical experience.[4] Thalassemia is a rare disease in the U.S., and there is a possibility that treatment standards developed for other conditions (aplastic anemia, sickle cell disease, chemotherapy-induced myelosuppression) could be applied erroneously to patients with thalassemia. Although the management of thalassemia has evolved, low provider expectations for physical and professional achievement may persist due to outdated information. Furthermore, physicians often identify concern over iron loading instead of anemia as the most important management issue in thalassemia.[4] Concern over donor exposure can also lead to using less than the recommended volume of blood. Transfusion guidelines for thalassemia should identity these barriers and provide solutions that can be used to educate providers and patients.

3.3 | Heterogeneity of transfusion-dependent thalassemia

In the past decade, the classification of patients into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) was widely adopted.[10] This nomenclature has proved useful in planning the management of iron overload or making decisions about stem cell transplantation. However, these terms can potentially hide the tremendous heterogeneity of TDT and NTDT. Beta thalassemia major caused by two severe β globin mutations is the largest subgroup within TDT.[53] These children usually become symptomatic during the first year of life and regular transfusions are instituted before 2 years of age.[15,42] The disease course for β thalassemia major is the best studied among TDT, and transfusion guidelines developed by various organizations are similar.[5,10]

There are other forms of TDT where the application of standards developed for β thalassemia major may not be appropriate. Conceptually, these entities can be thought of as severe β thalassemia intermedia. While these patients may require intermittent transfusions during infancy, such as during an illness, the institution of regular transfusions is often delayed until 3 years or later.[42] In a subgroup of thalassemia intermedia, transfusions are started in adult life in response to deteriorating quality of life or development of a complication from severe anemia.[22,23] Two main subtypes of thalassemia in

this category are β thalassemia intermedia and HbE β thalassemia, which differ from β thalassemia major in the capacity for hemoglobin synthesis and adaptation to anemia (see Section 2.3).[41]

4 | EXISTING TRANSFUSION GUIDELINES: SOURCES AND APPLICABILITY TO THALASSEMIA IN THE UNITED STATES

Guidelines for management have been published by the Thalassemia International Federation and other professional organizations.[5,10,54–58] However, since β thalassemia major has been the principal focus of these guidelines, there are limitations in their application to the U.S. thalassemia population with its prominent genotypic diversity. In contrast with many other countries, thalassemia in the United States is observed disproportionately among the immigrant communities.[6] Historically, the broad categories of ethnicities were Mediterranean and Asian (Southeast Asia and China), but to these should also be added South Asian and the Middle Eastern populations.[6] There are significant proportions of patients with HbE β thalassemia and α thalassemia, where the approach to chronic transfusions is distinct from β thalassemia major.[59–61] The red cell antigen disparity between donors and recipients is considerably greater due to differences in ethnicity, which amplifies the risk of alloimmunization.[9,62,63] On the other hand, the assured availability and safety of blood supply in the U.S. has led to an earlier adoption of chronic transfusions in more patients with β thalassemia intermedia and HbE β thalassemia compared with other countries.

4.1 | Decline of splenectomy in thalassemia

The gradual decline of splenectomy in thalassemia major has had a significant impact on transfusion management. An association between higher pre-transfusion hemoglobin levels and decrease in the rate of splenectomy has been documented.[52,64–66] This supports the clinical observation that development of splenomegaly in thalassemia is the consequence of maintaining low hemoglobin levels. Aiming for lower pre-transfusion hemoglobin can be counterproductive as it promotes splenic enlargement with a secondary rise in transfusion needs.[19,52] Caution is needed when referring to older transfusion guidelines developed in an era when most adults with thalassemia were splenectomized.

4.2 | Advances in iron chelation therapy

Transfusional iron overload is the most important complication of red cell transfusions in thalassemia, and the iron loading rate affects the efficacy of chelation therapy.[15,16,67,68] Until the availability of oral agents, the only available iron chelator was deferoxamine, which was difficult to use and had significant toxicity in young children.[69–71] These concerns about iron overload influenced the development of guidelines for transfusion therapy.[49,72] The management of iron overload has been transformed with the availability of oral chelators deferasirox and deferiprone, and the development of novel chelation regimens.[40,73] In current practice, transfusion volume and frequency should be selected based on the need to correct anemia and suppress marrow hyperplasia. A suitable chelation regimen can then be devised to maintain iron overload in the safe range.

5 | TRANSFUSION RECOMMENDATIONS FOR β THALASSEMIA

Ever since it was recognized that regular blood transfusions prolong the survival of children with β thalassemia major,[17] there were efforts to identify patients who should be placed on transfusions. Additional concerns included delineating optimum hemoglobin target and specification of RBC units and creating safe transfusion practices in individuals projected to have a normal life expectancy. Table 1 summarizes the pathophysiological and clinical features of β thalassemia that underlie these recommendations.

5.1 | Indications to start regular transfusions

The decision to initiate transfusions attempts to balance consequences from anemia and ineffective erythropoiesis against complications of chronic transfusion therapy.[19,49,74–79]

The paradigm of an infant with severe, symptomatic anemia who requires transfusions for survival served as the historical foundation of transfusion guidelines for β thalassemia major.[17,74,79] These high-risk infants have a combination of β^0 and/or severe β^+-globin gene mutations and should be identified through newborn screening. Early access to specialty care is essential so that the decision to commence transfusions can be made at the appropriate time to support normal growth and development (Table 1).[66,80,81] Nearly 50% of such infants

TABLE 1 Principal attributes of β thalassemia pertinent to developing recommendations for transfusion therapy

Features	Impact on transfusion therapy
Disease characteristics	
• Endogenous hemoglobin production is influenced by the severity of β globin mutations, co-inheritance of α thalassemia, and genetic variants linked to HbF production	• Baseline hemoglobin level and tolerance to anemia affect the age at which transfusions are initiated
• Hemoglobin composition (proportion of HbF) alters oxygen affinity of blood and shapes the adaptation to anemia	• These factors influence optimal pre-transfusion hemoglobin level and transfusion frequency for individual patients
• Low hemoglobin level is associated with ineffective erythropoiesis, bone marrow hyperplasia, increased intravascular volume	• Maintain hemoglobin level that averts skeletal changes and extramedullary hematopoiesis
Patient characteristics	
• Anemia leads to poor growth in children and frequent fatigue in adults	• Hemoglobin target may require adjustment in individual patients due to fatigue or pain
• Splenomegaly increases the volume of RBC transfusion necessary to maintain optimal hemoglobin level	• Prevention of splenic enlargement is a goal of transfusion therapy. In non-transfused patients, rapid enlargement of spleen is an indication to initiate transfusions
• Risk of alloimmunization is increased when transfusions are started later in life	• RBC genotype should be obtained at diagnosis for all patients
• Certain complications require modification of transfusion goals	• Higher hemoglobin threshold for patients with heart failure or extramedullary hematopoietic masses
Type of RBC product and matching	
• Disparity of red cell antigens between donors and recipients is greater in a multi-ethnic population	• Risk of alloimmunization is reduced with phenotypic matching. Genotyped donor registry improves access to matched units
• Alloantibodies may be evanescent and antibody screen can become negative with time	• Re-exposure to sensitized antigens can cause hemolytic transfusion reaction
• Transfusion requirements are affected by hemoglobin increment and red cell survival	• Prefer RBC units with higher hemoglobin content, short duration storage, and without irradiation
Other factors	
• Development of transfusional iron overload poses a risk for serious complications	• Use effective chelation regimens to control iron overload instead of lowering pre-transfusion hemoglobin target
• Lack of communication between hospitals increases the risk of transfusion reactions	• Centralized database of patients can prevent the transfusion of inappropriate units

receive their first transfusion by 6 months and 80% by 12 months of age.[42] When patients identified through newborn screening have care established before the development of severe symptoms, the time to initiation of transfusions is expected to be shorter.

Conversely, when affected individuals preserve significant endogenous hemoglobin synthesis, the decision for starting transfusions can become complex.[22,23,61,82] Such patients have thalassemia intermedia and can survive without being transfused at regular intervals. In the past, despite the compromised growth and quality of life,[83] it was felt that the consequences of a lifetime of regular transfusions were more serious.[22,23] Since many complications are delayed until adult life (chronic pain, fractures, thrombosis, and pulmonary hypertension),[22,23,25,84,85] physicians making the initial decision to withhold transfusions from patients with thalassemia intermedia are disconnected from those who manage them as adults. The use of splenectomy in children to avoid transfusions has been a particular predicament as the risk of several serious complications becomes manifest only later in adult life.[21,24,62,65,86–91] Over the past 3 decades, the long-term consequences of withholding transfusions from patients with severe thalassemia intermedia have become apparent, and this experience is being used to guide the development of the current standards of care.[22,23,84,92] These patients should be seen at 3–4 month intervals to determine whether it is appropriate to continue follow up without transfusions (Table 2).

TABLE 2 Criteria for initiation of regular transfusions

1. Hemoglobin <7 g/dl on 2 occasions at least 2 weeks apart
   a. β thalassemia major: <7 g/dl on 2 occasions, with or without symptoms
   b. HbE β thalassemia: <7 g/dl on 2 occasions and one or more of the symptoms listed in Section 3
2. Hemoglobin ≥7 g/dl, with one or more of the following symptoms
   a. Growth delay:
      i. Infants (<2 years): failure to gain weight for 3 months without another etiology
      ii. Children: Height velocity <3 cm/year
      iii. Delayed onset of puberty: >12 years in females, >13 years in males, with endocrine evaluation
   b. Skeletal facial changes: subjective, photographic record, discuss with patient and family
   c. Splenomegaly: Spleen >6 cm, or enlargement >1 cm/year after 2 years of age
   d. Extra-medullary hematopoiesis: symptomatic or moderate to severe EMH
   e. Cerebrovascular: overt stroke, silent infarcts, arterial narrowing, moya moya
   f. Venous thrombo-embolism
   g. Pulmonary hypertension
   h. Osteoporotic fracture
   i. Poor quality of life in adults: decline in capacity to work or perform usual activities

5.2 | Hemoglobin target, volume, and rate

The intensity of transfusion therapy for thalassemia is evaluated using the pre-transfusion hemoglobin level. There has been an evolution of the target hemoglobin over the years to balance improvement in anemia and ineffective erythropoiesis with transfusional iron overload [5,10,49,72,93] An adequate pre-transfusion hemoglobin level was initially estimated by improvement in growth and activity in young children,[17,18,79] which led to regimens that maintained hemoglobin above 9 or 9.5 g/dl.[19,49] More intensive regimens that kept the pre-transfusion hemoglobin in the normal range (>12 g/dl) were developed,[93,94] but concern for greater iron overload from increased blood use prompted moderation of the hemoglobin target.[19,49,72]

Prevention of splenomegaly should be the goal of an effective transfusion regimen, thereby mitigating the adverse effects of potential splenectomy. Another approach to determine the adequacy of transfusions is the suppression of marrow activity, which is achieved by maintaining pre-transfusion hemoglobin between 9 and 10 g/dl.[37,38,95] Reticulocyte count does not have a consistent relationship with pre-transfusion hemoglobin, though circulating nucleated red blood cells are suppressed at higher hemoglobin levels.[38] In general, children respond well with mean pre-transfusion hemoglobin 10 g/dl and a range of 9.5–10.5 g/dl, which prevents splenic enlargement and skeletal changes while promoting normal growth.[49,65,96,97] Certain patients who experience significant fatigue or skeletal pain toward the end of the transfusion cycle may benefit from a higher hemoglobin target.

Individuals with severe β thalassemia intermedia and HbE β thalassemia may initially require only intermittent transfusions, often during an illness causing acute worsening of the baseline level of anemia.[22] The institution of regular transfusions for these groups may be delayed until children are older than 3 years, or even later until adulthood as a response to deteriorating quality of life or complications listed in Table 2.[22] Many such patients may tolerate a less intensive regimen using a lower pre-transfusion hemoglobin range of 9–10 g/dl.

The volume of blood transfused is influenced by the interval between transfusions, with those on a 4-week schedule receiving a larger volume compared with those on a 3-week schedule to attain a similar pre-transfusion hemoglobin target.[49] Transfusion volume also depends upon the type of storage solution, since red cell units stored in additive solution have lower hematocrit.[98] The effect of the pre-transfusion hemoglobin target on the transfusion volume is not clear in the current era where splenectomy is no longer a frequent procedure.[93] Maintaining a higher hemoglobin can reduce the intravascular volume to allow a greater post-transfusion hemoglobin increment from a unit of RBC.[52,99,100] On the other hand, low pre-transfusion hemoglobin levels can cause a poorer post-transfusion increment through enlargement of the spleen and expanded peripheral and bone marrow intravascular space. In current practice, when most patients retain their spleen, the pre-transfusion hemoglobin level to achieve the optimal balance between post-transfusion increment and iron loading is not well defined.

The interval between transfusions will determine the amplitude of change in hemoglobin from the peak post-transfusion value to the level before the next transfusion. A study in adults receiving chronic transfusions for myelodysplastic syndrome linked lower hemoglobin amplitude to better quality of life,[101] but more frequent transfusions create inconvenience for patients and also burden the health system.

The rate of blood administration is of great relevance to outpatient RBC transfusion programs, as patients and providers share an interest in the shortest duration of transfusion that is safe. A rate of 5 ml/kg/h has been traditionally used in patients without cardiovascular compromise, which allows transfusions to be completed in a half day. In adults, a rate of administration up to 1 unit

TABLE 3 Recommendations for hemoglobin target, volume, and rate

1. Target hemoglobin
a. β thalassemia major: Pre-transfusion hemoglobin of 10.0 g/dl, range 9.5–10.5 g/dl
b. E β thalassemia: Pre-transfusion hemoglobin of 9–10 g/dl
2. Frequency of transfusion
a. Every 3 weeks in most older children and adults with β thalassemia major
b. Every 4 weeks
i. Younger children with β thalassemia major
ii. Most children and adults with E β thalassemia
c. It is preferable to change the volume of blood instead of the interval of transfusion to maintain hemoglobin target
3. Volume of transfusion
a. Children: Transfuse 4 ml/kg per gram increase in hemoglobin desired. The calculation uses post-transfusion hemoglobin of 13 g/dl on 3-week and 14 g/dl on 4-week schedule
b. Adults: 2, 3 or 4 units per transfusion. Generally: 3 units if pre-transfusion hemoglobin <10 g/dl, and 2 units if pre-transfusion hemoglobin ≥10 g/dl
4. Other volume considerations:
a. Patients with intact spleen have higher transfusion needs; Splenectomy is not recommended unless under exceptional circumstances
b. Adults with body weight > 60 kg may need 4 units on some transfusions
c. Higher hemoglobin target or transfusion more frequent than every 3 weeks are needed in rare circumstances
i. Congestive heart failure
ii. Pulmonary hypertension
iii. Symptomatic extramedullary hematopoietic masses
iv. Occurrence of fatigue or bone pain in pre-transfusion period
5. Rate of transfusion
a. Children: 5 ml/kg/h
b. Adults: 200–300 ml/h, based on tolerance
c. Congestive heart failure: Reduce volume and rate based on cardiac function

per hour can be tolerated. Volume of transfusion at a single visit is usually limited to a maximum of 20 ml/kg, though higher volumes have been used.[79] These recommendations are summarized in Table 3.

5.3 | Type of RBC product

Regular RBC transfusions present substantial risks to individuals with thalassemia that are additive due to the repeated lifelong exposure.[4,9,76,102] Transfusion reactions, ranging from mild to fatal, can compromise the management of thalassemia. Several donor parameters impact the efficacy of transfusion (hemoglobin increment), such as donor age, sex, and hemoglobin concentration.[103] Leukoreduction is essential to prevent febrile non-hemolytic transfusions and should be done by filtration in the pre-storage period.[104] When citrate phosphate dextrose-adenine is used as the anticoagulant-preservative unit, the hematocrit of the final unit is 65%–80% and the volume 250–300 ml. More commonly, units are stored with additive solutions which yield longer shelf life but have lower hematocrit of 55%–65% and higher volume of 300–350 ml.[105,106] Apheresis-derived units are not recommended for transfusions in adults due to smaller hemoglobin increments.[103,105] Patients who demonstrate recurrent allergic reactions should be given washed units using a process that minimizes loss of blood.[107] Administration of antihistamine or steroid prior to transfusion is a less preferable alternative to washing for patients on chronic transfusions.[108]

The age of the unit at transfusion is an important consideration due to the impact of the storage lesion on red cell survival.[109–111] In this respect, chronic transfusion regimens differ from acute transfusions where hemoglobin increment at 24 h is the primary consideration, and relatively unaffected by the length of storage.[103] It is not known how RBC recovery is different in thalassemia with increased destruction of damaged RBC in the spleen, or if the increase in non-transferrin-bound iron is detrimental.[112–114] Storage duration has a negative impact on hemoglobin measured prior to next transfusion,[115] which potentially increases transfusion need and iron loading. Although transfusion of fresh RBC unit may be desirable, it must be balanced with the need for inventory management and procurement of rare blood types. Where possible, RBC units for transfusion in thalassemia should be considered special use and should not have to conform to "first-in-first-out" practice. There is a specific concern over the collective impact of prolonged (>14 days) storage and irradiation on RBC recovery following transfusion.[116,117] Progression of the radiation-induced damage to RBC membrane in the recipient following transfusion is currently unknown, as is the potential for increased splenic clearance of red cells with membrane lesion and low cellular adenosine triphosphate content.[112] Irradiation of RBC units for thalassemia is redundant and probably detrimental,[118] but becoming more common with the adoption of universal irradiation of blood components by institutions. The optimization of component characteristics is vital for quality of transfusions in thalassemia where most donor and recipient factors are fixed.[119]

5.4 | Extended matching for red blood cell antigens

Prevention of red cell alloimmunization is an important goal of transfusion management in thalassemia.[120] However, restricted blood availability can arise if the aim is to provide extended antigen-matched blood to all patients. Since anti-Rh and anti-Kell are the most common alloantibodies observed in thalassemia,[4,9,62,63] the vast majority of antibody formation can be prevented by universal provision of Rh/Kell matched blood.[121,122] Unfortunately, there is a worrisome lack of consensus about prophylactic Rh/Kell matching for the prevention of alloimmunization.[9,58,123–125] Patients who develop one alloantibody are at high risk for developing subsequent alloantibodies and/or an autoantibody.[4,9,126] These patients should receive RBC units with phenotypic matching (Rh, K, Jk, Fy, and MNS). Meticulous antibody history is essential for all patients, since an antibody screen can become negative with time in the absence of antigenic exposure.[127,128] Patients with a history of antibody must continue to receive antigen-negative blood to prevent acute and delayed hemolytic transfusion reactions.[129–131] RBC genotyping should be performed as part of the initial assessment of a patient who may require transfusions. RBC genotyping is feasible for recently transfused patients and has the advantage of detecting variant antigens. It is also a useful reference when investigating the development of an alloantibody to a very rare or very common antigen or in the presence of an interfering substance, such as an autoantibody or medication.[132,133] The development of registries consisting of donors with RBC genotyping will improve access to red cell units for patients with multiple antibodies. (Table 4).

TABLE 4 Specification of RBC units for thalassemia

1. Leukoreduced PRBC: Pre-storage leukoreduction
2. Storage: Additive solution (hematocrit 55%–60%) or CPD-A (Hct 70%–75%)
3. Age of unit: Less than 2 weeks where possible
4. Washed RBC units: For patients with severe allergic reactions
5. Irradiation of RBC units is unnecessary
6. Phenotypic matching: Recommended minimum antigen matching
a. Patients lacking alloantibody: Match to Rh/K
b. Patients with one or more alloantibody: Match to Rh/K/Jk/Fy/S

5.5 | Other recommendations

Thalassemia is a rare disease in the U.S. where the expertise for management is concentrated in specialty centers in a few large metropolitan areas.[5] It is recommended that transfusion therapy should be directly supervised by a hematologist with expertise in thalassemia. Where this is not possible due to the distance from a specialty center, the transfusion plan should be devised and periodically reviewed by a hematologist with expertise in thalassemia. Options for stem cell transplant should be discussed soon after the diagnosis is confirmed and disease modifying therapies should be offered where appropriate. It is necessary to develop thalassemia-specific protocols for patients receiving regular RBC transfusions to ensure optimal long-term outcomes.[10,19,60,67] In the absence of a national blood service, electronic health records offer several opportunities for consistency and quality assessment in transfusion medicine.[134] The indication for use of RBC units should be clearly identified as thalassemia for proper communication between ordering physician and blood bank. An accurate record of transfusion volume at each visit must be maintained, which can be then used to calculate annual transfusion requirement and iron loading rate.[19] Development of iron overload should be evaluated with serial ferritin measurements after the first 6 months of transfusions. When patients are transfused at multiple facilities, antibody history must be obtained from other hospitals and documented in patient's record.[135] The lack of a centralized database containing recipients of chronic transfusions is a serious shortcoming[136] as patients may receive transfusions at multiple hospitals[4] for reasons related to changes in insurance providers, transition of care to adult service, proximity to a center for urgent transfusions, and mobility for education or employment. Patients receiving regular or intermittent transfusions should be entered into a county- or state-level registry which can then be interlinked to develop a national database. Such an endeavor should be promoted by federal health agencies as a quality-of-care metric for transfusion management of thalassemia, sickle cell disease, and other transfusion-dependent anemias.

ACKNOWLEDGMENTS

The authors thank Sujit Sheth, MD, Harold Weill Professor of Pediatric Hematology, Weill Cornell Medical College, New York, for critical review and suggestions on the manuscript. The authors wish to thank Meghan Foe, BA, for providing organizational support to the Thalassemia Western Consortium and editorial assistance with the review of literature. This project is supported by the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services (HHS)

as part of a financial assistance award totaling $250,000 with 0 percentage financed with non-governmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by CDC/HHS, or the U.S. Government. This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $200,000 with 0 percentage financed with non-governmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government. For more information, please visit HRSA.gov.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lal A, Wong T, Keel S, Pagano M, Chung J, Kamdar A, et al. The transfusion management of beta thalassemia in the United States. Transfusion. 2021;61:3027–39. https://doi.org/10.1111/trf.16640