Background: In the absence of curative treatment, such as stem cell transplant, regular transfusions remain the mainstay of therapy for individuals with thalassemia major, a syndrome that results from marked ineffective erythropoiesis and the resultant anemia. The primary objectives of transfusion therapy are twofold: to suppress ineffective erythropoiesis and to ensure appropriate growth and development through childhood. In practice, a number of different transfusion protocols are in use across the developed world, with on-demand transfusion still being the paradigm in most of the developing world with limited resources.

Study Design and Methods: To investigate perceived differences in transfusion practice, a self-reported electronic survey was disseminated to eight US thalassemia treatment centers in February 2011. The survey was divided into sections ranging from laboratory and clinical practices to emerging transfusion-transmitted diseases.

Results: The survey response rate was 100%. The total number of transfused patients was 411. One-hundred percent of institutions used leukoreduced blood. No centers routinely provided cytomegalovirus-seronegative red blood cells (RBCs). Half the centers provided irradiated RBCs; only one routinely provided washed RBCs, and none transfused RBCs of defined storage age. Seventy-five percent of centers routinely phenotyped thalassemia patients’ RBC antigens; 50% prophylactically matched for Rh and K antigens. The frequency of antibody investigations varied widely, and 25% of centers routinely medicated patients before transfusion.

Conclusion: Eight thalassemia centers in the United States were surveyed to determine the uniformity of transfusion practice. The variability of the results was surprising. Consequently, we performed a literature review and propose an evidence-based protocol for routine transfusion therapy for patients with thalassemia.

Abbreviation: TTC(s) = thalassemia treatment center(s).

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alloimmunization, immunomodulation, transfusional iron overload, and the effect of prolonged red blood cell (RBC) storage age have come into focus. Despite the established success of a transfusion regimen for thalassemia patients, specific guidelines for the appropriate selection of RBC components with regard to storage age, product modification requirements, and RBC donor-recipient antigen matching requirements are not available. In the United States there is variability in the manner of the regular transfusion regimen, from the time of initiation, the target hemoglobin (Hb) level, the type of matching, the testing performed, and the type of actual product administered.

We conducted an electronic survey and a literature review in an attempt to ascertain the consistency of current transfusion practice for patients at eight large thalassemia treatment centers (TTCs) across the United States. Our survey highlights the variability of transfusion practice, and based on a literature review we propose an evidence-based protocol for regular transfusion therapy for patients with thalassemia major.

MATERIALS AND METHODS

A 23-question self-administered electronic survey was disseminated to the six members of the Thalassemia Clinical Research Network and two additional TTCs to represent geographic diversity in February 2011 (Appendix S1, available as supporting information in the online version of this paper). The survey was designed and written by a transfusion service medical director and administered to a thalassemia clinic medical director and nurse practitioner and a pathology resident for validation purposes. The results of the validation survey were uniform for all participants and consistent with institutional practice. All agreed that the questions were to the point with little chance for misinterpretation and that no further validation was necessary.

The transfusion service directors of eight academic TTCs, representing geographically diverse locations (Southeast, Northeast, West Coast, and the Midwest), were initially notified of the voluntary survey via telephone. Phone notification included the intent and a brief description of the survey. Verbal communication was followed by an e-mail with a link to a Web site (http://SurveyMonkey.com) with an electronic version of the questionnaire. All data obtained from the survey were collected anonymously.

The survey consisted of six sections: Question 1 inquired about the number of chronically transfused thalassemia patients at each institution. Questions 2 through 7 requested information on RBC modifications (e.g., leukoreduction), RBC storage age, and storage solutions. Questions 8 through 14 asked respondents to identify practices surrounding RBC genotyping and phenotyping. Questions 15 through 17 inquired about transfusion-transmitted diseases in thalassemia populations, including babesiosis. Question 18 concerned the routine use of a direct antiglobulin test (DAT) for thalassemia patients. Questions 19 through 23 approached issues regarding clinical practice style including transfusion indications and pretransfusion medication. No questions on the survey were mandatory and each could be left blank. To further discourage respondents from guessing, many questions included an “I don’t know” or “other” response option that included an area for entering free text.

Statistical analysis
The main objective of the survey was to describe the current laboratory and transfusion practices employed by thalassemia centers in the United States. Therefore, our analysis of results was primarily descriptive in nature using computer software (Excel 2008, Version 12.2.6, Microsoft Corp., Seattle, WA). Free-text responses were descriptively listed or interpreted and summarized by the authors. As this survey was directed at querying departmental practices only and did not include any specific patient information or contact, institutional review board approval was not required.

RESULTS
All eight TTCs participated in the survey (100% response rate). The surveys were completed over 1 year. Six surveys were completed as a self-administered questionnaire. Two surveys were interviewer assisted when the authors followed up on the nonresponsive centers with a phone call. The interviewer read the questions verbally to the participants and recorded the responses verbatim into the online questionnaire. During the verbal communication, no guidance or interpretation of the questions was provided. All eight surveys were deemed evaluable based on a high response rate for each question (Table 1). The survey had 23 questions, and the average response rate of institutions for all questions was 83.5% (range, 50%-100% per question). Since not all participants responded to each question, the summarized data include the number of respondents for each question in parentheses. The surveys were completed by a transfusion medicine director, transfusion medicine manager, or a thalassemia nurse practitioner.

RBC modifications
Collectively, eight institutions reported responsibility for 411 regularly transfused thalassemia patients. One-hundred percent of the TTCs provided leukoreduced RBCs to their thalassemia patients. Half of the centers routinely provided irradiated RBCs. Only one of eight responders
(12.5%) routinely provided all thalassemia patients with washed RBCs. Seven centers indicated that they transfused washed RBC units for specific indications, for the prevention of recurrent allergic reactions, while one center also specified washing as an additional means of removing white blood cells (WBCs). One center reported the use of volume reduction for volume-sensitive patients. No centers routinely provided cytomegalovirus (CMV)-seronegative RBCs, neocytes (fresh RBCs), or frozen thawed units. Five institutions provide RBCs without regard to storage age (Fig. 1), with the other three attempting to give fresh blood (less than 14 or 21 days) whenever possible. Three institutions use RBCs stored in additive solutions (ASs) only, while five reported the use of both CPDA-1 and ASs.

Six responders (85.7%) reported that thalassemia intermedia patients receive the same RBC modifications as thalassemia major. One responder reported that these patients are not treated the same as thalassemia major but did not provide additional details.

**RBC genotyping or phenotyping**

Seventy-five percent of responders reported phenotyping or genotyping at the first patient encounter, while 100% of responders reported that sickle cell patients are routinely phenotyped or genotyped. One center reported phenotyping or genotyping a patient only once they developed a positive antibody screen. Half (50%) of responders routinely match RBC units for the Rh (C, c, E, e) and K1 (Kell) RBC antigens. Two centers commented that if antibodies develop they provide more extensive matching (e.g., Duffy/Kidd). Half of the responders perform their own RBC genotyping and the rest send the samples to a reference laboratory.

**Antibody investigations and DAT**

The frequency of performing antibody investigations when an antibody screen is positive for thalassemia patients not receiving phenotype- or genotype-matched RBC units varied widely between institutions (Table 2). For patients receiving phenotype- or genotype-matched RBC units, half of the centers will only perform an investigation if there is a change in the antibody screen while others repeat it routinely once every 3 or 6 months. DAT is performed during each antibody investigation at 50% of institutions and 50% only when an autoantibody is detected.

**Transfusion-transmitted disease**

Three centers (37.5%) reported at least one case of transfusion-transmitted babesiosis at their institution.
Do patients routinely get transfused if they are below a specific Hb level?

- 8 g/dL: 15%
- 9 g/dL: 15%
- 10 g/dL: 42%
- Patient Dependent: 29%

Fig. 2. Minimum Hb transfusion threshold for thalassemia patients.

How many units do you routinely transfuse per transfusion episode?

- 3 units: 13%
- 2 units: 12%
- Based on pretransfusion Hb: 25%
- Based on patient's baseline Hb: 50%

Fig. 3. Dose of RBCs transfused per episode.

What volume is used for pediatric RBC transfusions?

- 15 mL/kg: 17%
- 10 mL/kg: 17%
- Volume based on pretransfusion Hb: 33%
- Volume based on clinical situation: 33%

Fig. 4. Volume of RBCs transfused per episode in pediatric thalassemia patients.

Are thalassemia patients routinely medicated before transfusion?

- No: 14%
- Yes, always: 29%
- Yes, if they have had a previous reaction: 29%
- Yes, but only for significant urticarial reactions: 29%

Fig. 5. Routine use of pretransfusion medication in thalassemia patients.

Within the past 5 years; two of three are in regions endemic for babesiosis. When questioned about other emerging infectious diseases, the majority of participants did not respond.

Current clinical transfusion practices

Most centers have specific threshold Hb levels at which thalassemia patients are transfused (Fig. 2), while one center reported that it is patient dependent. The dose of RBCs transfused was a standard 2 or 3 units or dependent on the pretransfusion Hb (Fig. 3). The dose most frequently reported for pediatric patients was 10 mL/kg (Fig. 4). No center obtains a posttransfusion Hb level. Twenty-five percent of institutions reported routinely medicating patients before transfusion (Fig. 5).

DISCUSSION

The institution of a lifelong transfusion regimen in thalassemia patients is a well-established treatment for preventing the morbidity associated with severe anemia. The survey, the first of its kind in the United States, highlights the marked differences in practice at the different treatment centers surveyed. While the Thalassemia International Federation has posted recommendations on its Web site, there are no other published, evidence-based guidelines for the optimal transfusion of thalassemia patients and no guidelines on the use of RBC modifications and specific pretransfusion testing. After an extensive review of the literature, we propose the following as evidence-based guidelines for a regular transfusion program for patients with transfusion-dependent thalassemia. Although not all of the literature cited is specific for the thalassemia population, we based recommendations on literature from the general transfusion literature only where appropriate.

RBC modifications

Leukoreduction

Leukoreduction decreases the number of contaminating WBCs in the final blood component. Current third-generation blood filters are able to achieve a 3-log reduction (99.9%) of WBCs in cellular components. Clinical
studies have documented that the use of leukoreduced blood products can decrease the frequency of a number of complications associated with RBC transfusion, most importantly febrile reactions, alloimmunization, and transmission of certain infections.8

Febrile nonhemolytic transfusion reactions are a frequent complication and can lead to additional costly medical interventions such as antipyretic and/or antibiotic usage as well as blood product wastage.9 The use of leukoreduced RBCs has been shown, in the general transfused population as well as in thalassemia patients specifically, to significantly reduce the incidence of febrile nonhemolytic transfusion reactions.9-14

While the use of leukoreduced RBCs has also been shown to decrease the incidence of WBC alloimmunization in a number of prospective randomized trials in immunocompromised patients, there are no clinical studies showing the same results in an immunocompetent population.8 Given that thalassemia patients require lifelong RBC transfusions, minimizing alloimmunization would be beneficial. Furthermore, with advances in stem cell transplantation and the advent of gene therapy, alloimmunization could have a detrimental effect on outcomes of these procedures as well.

**CMV status**
CMV resides within WBCs and transfusion of infected cells can cause primary infection in recipients that are CMV seronegative. To prevent transfusion transmission of this infectious agent, either leukoreduced or CMV-seronegative blood products have been utilized. A pivotal article by Bowden and colleagues in 199515 demonstrated that the incidence of CMV transmission was comparable for both recipients of leukoreduced blood components and recipients of CMV-seronegative blood components (2.4% vs. 1.3%). In the past, there has been debate about the conclusion in this study and subsequent reports of transfusion transmission rates as high as 6.5% from leukoreduced products have been reported.16 However, recent reports in severely immunocompromised populations, such as stem cell transplant recipients, have found very low risk of using leukoreduction instead of units from CMV-seronegative donors.17 Any remaining residual risk for CMV transmission is only a concern for immunocompromised patients, since primary CMV infection in immunocompetent patients is usually asymptomatic with little-associated morbidity or mortality.18,19 Therefore, the use of leukoreduced blood products to reduce the risk of transfusion-transmitted CMV is an acceptable choice in the thalassemia population.

**Washing**
Washing of cellular components before transfusion removes more than 99% of the extracellular fluid in the product. The process removes most of the plasma proteins and the original supernatant, which may contain unwanted substances (e.g., anticoagulant-preservative solution, cytokines, electrolytes). However, upward of 20% of the original number of RBCs can be lost during the process, and overall RBC quality is compromised as well.20 Therefore, the use of this product is limited to a few specific indications, namely, 1) in patients who have severe recurrent allergic or anaphylactic reactions that cannot be prevented medically with the use of antihistamines and/or steroids and 2) for the prevention of hyperkalemia or cardiac arrhythmia in small children undergoing massive transfusion (>25 mL/kg). In a patient population dependent on the amount of Hb transfused during each instance it would not be advantageous to infuse an inferior product without good reason. In our survey, only one center reported routinely washing RBCs before transfusion, while the remainder restricted the use of washed products to patients who have had recurrent severe transfusion reactions.

**Irradiation**
Gamma irradiation of cellular components renders lymphocytes incapable of proliferation and engraftment. The only indication for irradiation is the prevention of transfusion-associated graft-versus-host disease. There is no definitive indication for all thalassemia patients to receive irradiated products, especially since there is some compromise in the product quality after irradiation (increased extracellular potassium and free Hb). In large institutions with high numbers of immunocompromised patients, the blood bank may irradiate all cellular components at the time of issue to avoid the expense and difficult logistics of maintaining a dual inventory. Interestingly, half of the TTCs surveyed reported the regular use of irradiated RBCs, most likely as a result of a blood bank policy for irradiating all cellular components issued.

**RBC storage**
RBCs can be stored in a variety of Food and Drug Administration (FDA)-approved solutions with varying lengths of storage and final hematocrit (Hct; Table 3).21-25 A RBC unit stored in AS is the standard of care in the United States and there are no data or clinical reasons to suggest that AS should not be used for thalassemia patients. Five of the eight institutions reported the use of both CPDA-1 and ASs, while the remaining three used AS exclusively. This most likely reflects the current practices of the blood bank and not a practice related specifically to the thalassemia population.

There has been much recent interest in the in vivo effect of transfusing RBCs approaching the end of their shelf life.26 Data in mice and humans suggest that there is more rapid extravascular clearance of older RBCs.27-28 Some studies reported an inflammatory response in
human with older RBCs, while others did not. Nevertheless, there is evidence that levels of non–transferrin-bound iron are transiently elevated after infusion of older cells. This could have significant implications in patients who already have transfusional overloading and organ dysfunction secondary to iron deposition, where the added oxidative stress of this reactive iron species could lead to further damage. If data currently being collected confirm this in transfused patients with thalassemia, fresher units may be of benefit for this cohort, and similarly for other cohorts of regularly transfused patients.

**RBC genotyping or phenotyping**

RBC alloimmunization is a well-known complication and major challenge of regular transfusion in thalassemia patients. The rates of RBC alloimmunization vary widely; a recent US study of 697 transfused subjects with various forms of thalassemia found that 16.5% of individuals were alloimmunized. Significantly, the study confirmed that subjects who received blood phenotypically matched for Rh and Kell in addition to ABO had a lower rate of alloantibody development. This was also previously shown in a large Greek study. Alloimmunization remains a significant problem in the developing world where such phenotyping is not performed, and recent reports indicate incidence ranging from 7.7% in Tunisia to 28% in Egypt. Despite these data, our survey only half of the reporting institutions routinely provide Rh and Kell phenotypically matched units to their thalassemia patients. Interestingly, the majority of institutions are phenotyping or genotyping thalassemia patients at first encounter even if they are not providing antigen matched units. Presumably, the information could be used subsequently if a patient developed auto or alloantibodies. One limit to the usefulness of genotypic or phenotypic matching is the limited availability of compatible blood. Phenotypic matching limited to the Rh and K antigens may be easier to achieve than full matching for RBC antigens. The disadvantage of antigen matching is the delayed time to procure needed units, as well as additional cost and logistical considerations. Based on the discussion above, we recommend that thalassemia patients be genotyped or phenotyped (when possible) at first patient encounter and then receive units phenotypically matched for Rh D, C, c, E, e, and K to minimize the risk of alloimmunization.

**Antibody investigations and DAT**

Our survey results indicate that half the participating programs perform a routine DAT on the pretransfusion specimen, presumably as an indicator of early alloimmunization in addition to potential identification of a new autoantibody. In one study, more than half (52.5%) of the thalassemia patients had a positive DAT (IgG) with nonreactive eluates. This has been attributed to a number of factors including increased levels of IgG, hepatitis C virus (HCV) positivity, and sialic acid abnormalities in the RBC membrane. It is often difficult to determine whether the reactivity is clinically significant or merely evidence of nonspecific binding of IgG, which may interfere with routine pretransfusion testing, leading to an expensive and time-consuming investigation before each transfusion. We recommend monitoring of the pretransfusion Hb as a marker for the development of a new clinically significant autoimmune or alloimmune hemolysis to avoid the need for a DAT at each transfusion visit.

AABB Standard 5.13.3 clearly outlines the required frequency of antibody screening. However, the standards are not prescriptive with regard to the frequency for antibody investigations (specific identification of the RBC antibody in distinction from an antibody screen) and hospital policies vary widely as to how frequently they are performed. In a group of patients who are being regularly transfused, frequent antibody investigations can lead to the consumption of a significant amount of laboratory resources. The survey revealed that there is no practice consensus for the frequency of performing investigations in thalassemia patients. Responses ranged from performing antibody investigation before each transfusion event to performing investigations only once a year. Research and publication on the safest time interval would be valuable information for transfusion services that treat chronically transfused patients; however, based on currently available evidence, antibody identification should be performed every 72 hours when a patient has a positive antibody screen.

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**TABLE 3. Content of whole blood anticoagulant-preservative (mg/63 mL) and ASs (mg/100 mL)**

<table>
<thead>
<tr>
<th></th>
<th>CPD</th>
<th>CP2D</th>
<th>CPDA-1</th>
<th>AS-1 (Adsol)</th>
<th>AS-3 (Nutricel)</th>
<th>AS-5 (Optisol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean final Hct in unit (%)</td>
<td>65-80</td>
<td>65-80</td>
<td>&lt;80</td>
<td>55-65</td>
<td>55-65</td>
<td>55-65</td>
</tr>
<tr>
<td>FDA-approved shelf life (days)</td>
<td>21</td>
<td>21</td>
<td>35</td>
<td>42</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>1660</td>
<td>1660</td>
<td>1660</td>
<td>0</td>
<td>588</td>
<td>0</td>
</tr>
<tr>
<td>Citric acid</td>
<td>188</td>
<td>188</td>
<td>188</td>
<td>0</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>Dextrose</td>
<td>1610</td>
<td>3220</td>
<td>2010</td>
<td>2200</td>
<td>1000</td>
<td>900</td>
</tr>
<tr>
<td>Monobasic sodium phosphate</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>0</td>
<td>276</td>
<td>0</td>
</tr>
<tr>
<td>Adenine</td>
<td>0</td>
<td>0</td>
<td>17.3</td>
<td>27</td>
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<tr>
<td>Mannitol</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>750</td>
<td>0</td>
<td>525</td>
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<tr>
<td>Sodium chloride</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>900</td>
<td>410</td>
<td>877</td>
</tr>
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</table>
Transfusion-transmitted disease
Risks to the blood supply still exist from both emerging infectious diseases and diseases that lack adequate screening methods. Since regularly transfused patients are particularly vulnerable to these diseases due to their repeated exposure to blood products, questions related to transfusion-transmitted infections were included in this survey. The threat of infection by conventional transfusion-transmitted agents has been greatly reduced in developed countries; however, there are still ongoing, remote risks of human immunodeficiency virus, HCV, and hepatitis B virus in all countries. The estimated risk of transfusion-transmitted infection per unit transfused for each virus, respectively, is 1 in 1,467,000, 1 in 1,149,000, and 1 in 280,000. In addition emerging pathogens such as babesiosis, Trypanosoma cruzi, Coxiella burnetti, Creutzfeldt-Jakob disease, dengue, severe acute respiratory syndrome, and West Nile virus remain threats to our blood supply. One-third of responding centers reported recent cases of babesiosis. Many patients with thalassemia major are asplenic and especially vulnerable to babesiosis. In addition to the risk due to a tick bite in endemic areas, thalassemia patients are exposed to the risk associated with blood donors living in endemic areas. Pathogen reduction technology is an exciting alternative to prevent transfusion-transmitted infections. Although pathogen-reduced platelets (PLTs) and plasma are licensed in other parts of the world, no products are available yet in the United States.

Current clinical transfusion practices
Our study did not find consensus as to the threshold for transfusion, nor the trough Hb level maintained. While recent data are not available, studies from five decades ago showed that a hypertransfusion program aimed at maintaining a trough Hb of 10 g/dL was effective in promoting normal growth and development through childhood. However, recent data do confirm that this transfusion regimen effectively suppresses erythropoiesis and increases hepcidin levels, thereby ameliorating some of the related complications—bone changes, increased iron absorption, hepatosplenomegaly, and failure to thrive. Inadequately transfused patients, like those with the thalassemia intermedia syndromes, may continue to have these complications. Therefore, we recommend instituting a hypertransfusion regimen at diagnosis and continuing it until growth and development is completed in the second decade of life.

Our study also found variability in the volume of RBCs transfused at each visit, the rate of infusion, and the use of routine pretransfusion medication. With the goal of maintaining a trough Hb of approximately 10 g/dL, hypertransfusion protocols recommend transfusing 10 to 15 mL/kg RBCs at each visit. Given the risk of alloimmunization as previously discussed, minimizing exposure to multiple donors, a known risk factor, is important. Partial units are indicated only in very young children who would not be able to tolerate full units at one time. Consequently, we would recommend transfusing whole units and not splitting them. This may mean less frequent transfusions in early childhood (approx. 24-35 kg), progressing to more frequent visits as the child grows, until the child is approximately 48 kg, when 2 units may safely be administered at each visit. Therefore, the frequency of transfusion visits can vary in the first and early second decades of life, with the goal of maintaining the trough Hb level and transfusing whole units.

The routine use of pretransfusion medication with transfusion was reported by 25% of the responding centers. Historically, in an attempt to prevent the two most common transfusion reactions (febrile nonhemolytic and allergic), acetaminophen, diphenhydramine, or a combination of both was administered before transfusion. The practice was based on studies performed in the 1950s before the introduction of universal prestorage leukoreduction. The results of the only prospective, randomized, double-blind controlled trial examining the ability of empiric pretransfusion medication to reduce the incidence of any type of reaction after transfusion of blood products (RBCs and PLTs) only showed a significant advantage for reducing the risk of a febrile reaction (decrease by 52%). The authors went on to state that to prevent only one febrile reaction, 26 patients would unnecessarily be given medication. The study results do not support the practice of pretransfusion medication, especially in regularly transfused immunocompetent patients. Use of antipyretics and antihistamines carries its own inherent risks. Both first- and second-generation antihistamines cross the blood–brain barrier and may cause a number of adverse effects including sedation and blurry vision. A Dutch study in which an on-the-road driving test was used to assess impairment found equivalent impairment in persons treated with 50 mg of diphenhydramine and those with a blood alcohol content between 0.05 and 0.10% (in the United States, the legal blood alcohol content limit is 0.08% for drivers aged 21 or older). In developed nations, thalassemia patients are predominantly transfused in an outpatient setting and require safe transportation home at the completion of their infusion. We recommend pretransfusion medication only in patients who have had recurrent allergic or febrile nonhemolytic reactions in the past in conjunction with prestorage leukoreduced products.

In conclusion, Table 4 provides a summary of our proposed recommendations for a thalassemia transfusion protocol. We hope that the findings of our survey and our evidence-based recommendations will serve as a contemporary resource to help standardize the care of thalassemia patients in the United States.
ACKNOWLEDGMENTS

The authors sincerely thank all the survey participants for their time and knowledge.

CONFLICT OF INTEREST

The authors report no conflicts of interest or funding sources.

REFERENCES


TABLE 4. Summary of evidence-based recommendations

<table>
<thead>
<tr>
<th>Clinical transfusion practice recommendations</th>
<th>Laboratory recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Institution of a hypertransfusion regimen at diagnosis through completion of growth and development</td>
<td></td>
</tr>
<tr>
<td>• Maintain a trough Hb of 10 g/dL</td>
<td></td>
</tr>
<tr>
<td>• Transfusion of whole units of RBCs</td>
<td></td>
</tr>
<tr>
<td>• Hb level drawn before each transfusion</td>
<td></td>
</tr>
<tr>
<td>• Pretransfusion medication only in patients with recurrent allergic or febrile reactions</td>
<td></td>
</tr>
<tr>
<td>• Exclusive use of leukoreduced RBCs</td>
<td></td>
</tr>
<tr>
<td>• RBCs stored in AS is acceptable—42-day storage</td>
<td></td>
</tr>
<tr>
<td>• RBC phenotyping or genotyping on first encounter</td>
<td></td>
</tr>
<tr>
<td>• RBC units phenotypically matched for C, c, E, e, and K</td>
<td></td>
</tr>
<tr>
<td>• Extended phenotypic matching after alloimmunization</td>
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</table>

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article at the publisher’s Web site: Appendix S1. Thalassemia survey.