CLINICAL GUIDELINES

blood advances

American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

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Background: Red cell transfusions remain a mainstay of therapy for patients with sickle cell disease (SCD), but pose significant clinical challenges. Guidance for specific indications and administration of transfusion, as well as screening, prevention, and management of alloimmunization, delayed hemolytic transfusion reactions (DHTRs), and iron overload may improve outcomes.

Objective: Our objective was to develop evidence-based guidelines to support patients, clinicians, and other healthcare professionals in their decisions about transfusion support for SCD and the management of transfusion-related complications.

Methods: The American Society of Hematology formed a multidisciplinary panel that was balanced to minimize bias from conflicts of interest and that included a patient representative. The panel prioritized clinical questions and outcomes. The Mayo Clinic Evidence-Based Practice Research Program supported the guideline development process. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to form recommendations, which were subject to public comment.

Results: The panel developed 10 recommendations focused on red cell antigen typing and matching, indications, and mode of administration (simple vs red cell exchange), as well as screening, prevention, and management of alloimmunization, DHTRs, and iron overload.

Conclusions: The majority of panel recommendations were conditional due to the paucity of direct, high-certainty evidence for outcomes of interest. Research priorities were identified, including prospective studies to understand the role of serologic vs genotypic red cell matching, the mechanism of HTRs resulting from specific alloantigens to inform therapy, the role and timing of regular transfusions during pregnancy for women, and the optimal treatment of transfusional iron overload in SCD.

Summary of recommendations

Background

Transfusion support remains a key intervention in the management of patients with sickle cell disease (SCD). Red cell transfusions are used in the acute and chronic management of many complications related to SCD, but are not without adverse effects, including alloimmunization and iron overload. Specific indications, mode of red cell administration, and transfusion-related complications continue to pose significant challenges for patients and providers, and are the focus of these guidelines. The American Society of Hematology (ASH) guideline panel addressed specific questions related to the following areas: extent of red cell antigen typing and matching, transfusion indications and mode of administration

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(simple vs red cell exchange [RCE] transfusion), prevention and management of alloimmunization and delayed hemolytic transfusion reactions (DHTRs), and screening for iron overload.

These guidelines are based on updated and original systematic reviews of evidence conducted by the Mayo Clinic Evidence-Based Practice Research Program. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[1-4] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[5-11] to assess the certainty of the evidence and formulate recommendations.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation.

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action; only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and you must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their individual risks, values, and preferences.
- For policy makers: policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Recommendations

Red cell antigen profiling

RECOMMENDATION 1. The ASH guideline panel *suggests* an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before the first transfusion) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- An extended red cell antigen profile includes C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s at a minimum.
- Red cell antigen profiles should be made available across hospital systems.
- A serologic phenotype may be inaccurate if the patient has been transfused in the last 3 months.
- Genotyping is preferred over serologic phenotyping, as it provides additional antigen information and provides increased accuracy for, among other things, C antigen determination and Fy^b antigen matching.

Prophylactic red cell antigen matching

RECOMMENDATION 2. The ASH guideline panel *recommends* prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks:

- The extended red cell antigen profile may be determined by genotype or serology.
- Extended red cell antigen matching (Jk^a/Jk^b, Fy^a/Fy^b, S/s) may provide further protection from alloimmunization.
- Patients who have a GATA mutation in the *ACKR1* gene, which encodes Fy antigens, are not at risk for anti-Fy^b and do not require Fy^b negative red cells.
- Patients identified by genotype with the hybrid *RHD*DIIIa-CE (4-7)-D* or *RHCE*CeRN* alleles, which encode partial C antigen, and no conventional *RHCE*Ce* or **CE* allele should be transfused with C-negative red cells to prevent allo-anti-C development.

Prevention of hemolytic transfusion reactions in high-risk patients

RECOMMENDATION 3. The ASH guideline panel *suggests* immunosuppressive therapy (intravenous immunoglobulin [IVIg], steroids, and/or rituximab) over no immunosuppressive therapy in patients with SCD (all genotypes) with an acute need for transfusion and at high risk for acute hemolytic transfusion reaction or with a history of multiple or life-threatening delayed hemolytic transfusion reactions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- These are rare clinical situations in which patients are experiencing life-threatening anemia that requires immediate red cell transfusion and either compatible blood cannot be found (ie, patients with alloantibodies for whom antigen-negative blood is unavailable) and/or the patients have a history

of repeated episodes of severe hemolytic transfusion reactions with or without an antibody specificity identified (even when compatible blood is available).

- The hematologist and transfusion medicine specialist should have ongoing discussions to weigh the potential benefits and harms associated with transfusion vs the effect of ongoing life-threatening anemia and to consider the respective mechanisms of action for choice of therapy (IVIg, steroids, or rituximab).
- A shared decision-making process is critical.

Management of severe hemolytic transfusion reactions with hyperhemolysis

RECOMMENDATION 4. The ASH guideline panel *suggests* immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) over no immunosuppressive therapy in patients with SCD (all genotypes) with a delayed hemolytic transfusion reaction and ongoing hyperhemolysis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- A DHTR is defined as a significant drop in hemoglobin within 21 days posttransfusion associated with 1 or more of the following: new red cell alloantibody, hemoglobinuria, accelerated increase in percentage hemoglobin S (HbS%) with a concomitant fall in HbA posttransfusion, relative reticulocytopenia or reticulocytosis from baseline, significant lactate dehydrogenase (LDH) rise from baseline, and exclusion of an alternative cause.
- Hyperhemolysis is defined as a rapid hemoglobin decline to below the pretransfusion level and rapid decline of posttransfusion HbA level.
- Immunosuppressive therapy should be initiated promptly in patients with life-threatening hemolysis.
- The hematologist and transfusion medicine specialist should discuss potential benefits and harms associated with specific immunosuppressive therapies.
- First-line immunosuppressive agents include IVIg and high-dose steroids; the second-line agent is eculizumab. Rituximab is primarily indicated for potential prevention of additional alloantibody formation in patients who may require further transfusion.
- Depending on length of steroid therapy, weaning to avoid precipitation of a vaso-occlusive episode should be considered.
- Avoidance of further transfusion is recommended unless patients are experiencing life-threatening anemia with ongoing hemolysis. If transfusion is warranted, extended matched red cells (C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, S/s) should be considered.
- Supportive care should be initiated in all patients, including erythropoietin with or without IV iron.
- A shared decision-making process is critical.

Transfusion modality in patients with SCD requiring chronic therapy

RECOMMENDATION 5. The ASH guideline panel *suggests* using automated RCE over simple transfusion or manual RCE in patients with SCD (all genotypes) receiving chronic transfusions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The decision-making process should consider the clinical indication, baseline and target total hemoglobin and HbS%, patient age, patient preferences (particularly if central venous access is needed), iron overload status and iron chelation compliance, feasibility, and availability of compatible red cells.

Transfusion for patients with SCD and acute chest syndrome

RECOMMENDATION 6a. The ASH guideline panel *suggests* automated RCE or manual RCE over simple transfusions in patients with SCD and severe acute chest syndrome (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Automated RCE is preferred over manual RCE to more rapidly reduce HbS levels.
- Special equipment and trained staff are needed for automated RCE.
- Patients with small total blood volumes require a red cell prime because of the extracorporeal volume of the apheresis machine.
- A pre- and postprocedure complete blood count and hemoglobin fractionation should be obtained to maximize procedure safety and efficacy.

RECOMMENDATION 6b. The ASH guideline panel *suggests* automated RCE, manual RCE, or simple transfusions in patients with SCD and moderate acute chest syndrome (conditional recommendation based on very low certainty evidence in the evidence about effects ⊕◯◯◯).

Remarks:

- There is insufficient evidence to support automated RCE or manual RCE over simple transfusions in patients with SCD and moderate acute chest syndrome (ACS).
- Automated or manual RCE should be considered for patients (1) with rapidly progressive ACS, (2) who do not respond to initial treatment with simple transfusion, or (3) with high pretransfusion hemoglobin levels that preclude simple transfusion.
- Automated RCE can reduce HbS levels more rapidly than manual RCE.

Red cell exchange with or without isovolemic hemodilution for chronically transfused patients with SCD

RECOMMENDATION 7. The ASH guideline panel *suggests* either red cell exchange with isovolemic hemodilution (IHD-RCE) or conventional RCE in patients with SCD (all genotypes) receiving chronic transfusions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- IHD-RCE is a procedure available on some automated apheresis devices in which before the RCE, the patient undergoes a red cell depletion with concurrent volume replacement (normal saline or 5% albumin). The intent is to decrease the number of red cell units needed for the RCE.
- Consultation with a hematologist and transfusion medicine specialist is advised to assess safety for the individual patient and technical specifications.

- IHD-RCE is not advised for acute indications for RCE or when induction of further anemia during the IHD phase may be generally detrimental (eg, recent history of stroke or transient ischemic attack, severe vasculopathy, or severe cardiopulmonary disease).

Transfusion management during pregnancy

RECOMMENDATION 8. The ASH guideline panel *suggests* either prophylactic transfusion at regular intervals or standard care (transfusion when clinically indicated for a complication or hemoglobin lower than baseline) for pregnant patients with SCD (all genotypes) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- There is insufficient evidence to recommend a strategy of prophylactic transfusion rather than standard care.
- Prophylactic transfusion at regular intervals at the onset of pregnancy should be considered for women with:
  - a history of severe SCD-related complications before current pregnancy (including during previous pregnancies) to reduce recurrent pain episodes, incidence of acute chest syndrome, or other (SCD-related) comorbidities;
  - additional features of high-risk pregnancy (eg, additional comorbidities: other medical conditions or nephropathy).
- Women who develop SCD-related complications during the current pregnancy would benefit from initiating regular transfusion.

Preoperative transfusion for patients with SCD

RECOMMENDATION 9. The ASH guideline panel *suggests* preoperative transfusion over no preoperative transfusion in patients with SCD undergoing surgeries requiring general anesthesia and lasting more than 1 hour (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Decision-making should be individualized based on genotype, the risk level of surgery, baseline total hemoglobin, complications with prior transfusions, and disease severity.
- Clinicians should aim for total hemoglobin levels of more than 9 g/dL before surgery and should provide RCE transfusion for patients who require preoperative transfusion but have a high hemoglobin level (>9-10 g/dL) that precludes administration of simple transfusion.

Screening for transfusional iron overload

RECOMMENDATION 10a. The ASH guideline panel *suggests* iron overload screening by magnetic resonance imaging (MRI; R2, T2*, or R2*) for liver iron content every 1 to 2 years compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Validated R2, T2*, or R2* methods should be used; if they are not available, the patient should be referred to a specialized center.
- The same method (R2, T2*, or R2*) should be used over time.
- If patients are receiving iron chelation, MRI for liver iron content is helpful for titrating iron chelation, regardless of the ferritin level.
- If the ferritin level is less than 1000 ng/mL and the patient is receiving chronic transfusion by RCE with a neutral or negative iron balance, then MRI for liver iron content is likely not needed.

RECOMMENDATION 10b. The ASH guideline panel *suggests against* adding routine iron overload screening by T2* MRI for cardiac iron content compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The panel suggests that cardiac T2*MRI screening be performed for the subgroup of patients with SCD with a high iron burden (liver iron content >15 mg/g [dry weight (dw)]) for 2 years or more, evidence of end organ damage because of transfusional iron overload, or evidence of cardiac dysfunction.
- If cardiac T2* screening is performed, validated methods should be used and the same method should be used over time; if these methods are not available, the patient should be referred to a specialized center.

Values and preferences

These recommendations on transfusion support of patients with SCD placed a relatively high value on outcomes related to mortality, morbidity, progression of disease-related complications, and health-related quality of life. The panel recognized that there could be variability in the values and preferences related to these recommendations among patients and providers, depending on overall knowledge and education about any of the patient-important outcomes.

Explanations and other considerations

These recommendations take into consideration resource use, acceptability, feasibility, and effect on health equity. The ASH guideline panel acknowledged variability in patient and provider knowledge, as well as variability in their perceptions of harms vs benefits and other patient-important outcomes when developing these recommendations. Because of a lack of relevant data, cost-effectiveness of most interventions could not be assessed.

Introduction

Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations for red cell transfusion support in patients with sickle cell disease (SCD). These recommendations are intended to improve the judicious use of red cell transfusions, red cell matching, prevention and management of alloimmunization and DHTRs, and iron overload screening. Through improved provider and patient education of the available evidence and evidence-based recommendations, these guidelines can support shared decision-making that will enhance the benefits of transfusion while

minimizing associated harms, including alloimmunization and iron overload.

The target audience includes patients, hematologists, general practitioners, internists, other clinicians, and decision makers. Policy makers who may be interested in these guidelines include those involved in developing management plans for individuals with SCD. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem or problems

Most patients with SCD will have received a blood transfusion by the time they reach adulthood, either acutely for the management of SCD-related complications for preoperative preparation, or chronically to prevent neurologic and cardiopulmonary complications. The panel prioritized topics with (1) significant practice gaps or variability in transfusion management of patients with SCD, (2) the potential to affect the overall approach of transfusion support in SCD, and/or (3) the potential to guide challenging clinical decisions, such as management of severe HTRs or hyperhemolysis.

For patients with SCD, prevention of alloimmunization requires additional blood group antigen information (ie, extended typing). Whether the extended red cell antigen phenotype is obtained at the time of the first outpatient visit or just before the first transfusion, the extent of antigen typing and whether serologic or molecular methods are used varies among institutions. Similarly, despite national and international guidelines that suggest Rh and K matching (C, E, K or C/c, E/e, K antigens),[12,13] this is not practiced universally. For these reasons, the panel judged that a thorough evaluation of the published data and clinical guidance was necessary to assist patients and clinicians on these aspects of transfusion support for SCD.

Acute and delayed HTRs are among the most challenging complications of transfusion support in patients with SCD. The prevention and treatment of HTRs and hyperhemolysis with hemolysis of both the transfused red cells and the patient's own red cells may include supportive care, erythropoietin, IVIg, steroids, rituximab, eculizumab, and extending the degree of antigen matching. A priori, the panel acknowledged a paucity of high-certainty evidence, but judged that systematically reviewing the evidence from case reports and series could inform the recommendations on the use of immunosuppressive therapy for prevention or treatment of acute and delayed HTRs.

For patients with SCD requiring chronic transfusion therapy, the goal is to maintain the HbS% below a target threshold to reduce SCD-related complications. It is not well established whether patient outcomes are superior with manual or automated RCE vs simple transfusion, or with or without isovolemic hemodilution with automated RCE, where the patient undergoes a red cell depletion with concurrent volume replacement (normal saline or 5% albumin). Practice varies significantly according to institutional resources and expertise, and guideline recommendations may improve equity of care among patients.

Additional areas in which clinical equipoise exists or clinical interventions are not uniformly practiced include the roles of simple transfusion vs RCE for moderate or severe ACS, prophylactic transfusions for pregnant women with SCD, preoperative transfusion to prevent intra- and postoperative complications, and iron overload screening by MRI for liver or cardiac iron content. The panel's goal was to provide clinical decision support for shared decision-making by patients and clinicians based on the available evidence pertaining to these transfusion topics.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[5,7-11] The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the Guideline International Network-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html)[1] and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.[2,4]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with that of 4 other guideline panels (addressing other aspects of SCD) by ASH and the Mayo Clinic Evidence-Based Practice Research Program (funded by ASH under a paid agreement).[14] Project oversight was provided by a coordination panel, which reported to the ASH Guideline Oversight Subcommittee. ASH vetted individuals and appointed them to the guideline panel. The Mayo Program vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process, including the use of the GRADE approach.[14] The members of the guideline panel and the Mayo Program team are listed in supplemental File 1.

The panel included pediatric and adult hematologists and transfusion medicine specialists who all had clinical and research expertise on the guideline topic and a single patient representative. One cochair was a content expert; the other cochair was an internist and expert in guideline development methodology.

In addition to systematically synthesizing evidence and grading the evidence, the Mayo Program supported the guideline development process, including determining methods, preparing meeting materials, and participating in panel discussions of evidence. The panel's work was performed using a web-based tool (https://gradepro.org/) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings, but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representatives received honoraria of $100 per day for in-person meetings and $25 per conference call. The panelists received no other payments.

Table 1. Questions prioritized by the ASH Guideline Panel on Transfusion Support

Prioritized questions
Q1. Should an extended red cell antigen profile be obtained by genotype or serology vs only ABO/RhD type for patients with SCD?
Q2. Should prophylactic Rh (C, E, or C/c, E/e)- and K-matched red cells or prophylactic Rh (C, E or C/c, E/e)-matched, K-matched, and extended matched (Jk^a/Jk^b, Fy^a/Fy^b, S/s) red cells, by serologic or genotype-predicted red cell antigen profile, vs only ABO/RhD-matched red cells be used for patients with SCD receiving transfusions?
Q3. Should immunosuppressive therapy (IVIg, steroids, and/or rituximab) vs no immunosuppressive therapy be used for patients with SCD (all genotypes) with an acute need for transfusion and with a high risk for HTR?
Q4. Should immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) vs no immunosuppressive therapy be used for patients with SCD (all genotypes) with ongoing hyperhemolysis (defined as rapid decline of posttransfusion hemoglobin to below the pretransfusion level)?
Q5. Should automated RCE vs simple transfusion or manual RCE be used for patients with SCD receiving chronic transfusions?
Q6. Should automated or manual RCE be used over simple transfusion for patients with SCD and severe acute chest syndrome?
Q7. Should red cell exchange with IHD-RCE vs conventional RCE be used for patients with SCD receiving chronic transfusions?
Q8. Should prophylactic transfusion at regular intervals vs standard care (transfusion only when indicated for a complication or exacerbated anemia) be provided to pregnant patients with SCD?
Q9. Should preoperative transfusion vs no preoperative transfusion be used for patients with SCD undergoing surgeries requiring general anesthesia and lasting longer than 1 h?
Q10a. Should iron overload screening by MRI for liver iron content vs serial monitoring of ferritin levels alone be used for patients with SCD receiving chronic transfusion therapy?
Q10b. Should iron overload screening by MRI for cardiac iron content vs serial monitoring of ferritin levels alone be used for patients with SCD receiving chronic transfusion therapy?

Through the Mayo Clinic Evidence-Based Practice Research Program, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed through disclosure, panel composition, and recusal, according to recommendations of the Institute of Medicine[15] and the Guidelines International Network.[3] Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. The greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. A majority of the panel, including the cochairs, had no such conflicts. None of the Mayo-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was also used to manage conflicts of interest.[3,15-18] During deliberations about recommendations, any panel member with a current, direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context, but was recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) and the direction and strength of the recommendation. The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

In 2019, 4 panelists disclosed that during the guideline development process, they had received direct payments or other transfers of value from companies that could be affected by the guidelines. These disclosures occurred after the panel had agreed on recommendations; therefore, the individuals were not recused. Members of the Guideline Oversight Subcommittee reviewed the guidelines in relation to these late disclosures and agreed that the conflicts were unlikely to have influenced any of the recommendations.

Supplemental File 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years before appointment; in part B, they disclosed indirect financial interests; and in part C, other interests that are not mainly financial interests. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplemental File 3 provides the complete disclosure of interest forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel met in person and via conference calls to generate possible questions to address. The panel then used an iterative process to prioritize the questions listed in Table 1.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[19] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE approach.[19] Although acknowledging considerable variation in the effect on patient outcomes, the panel considered the following outcomes critical for clinical decision-making across questions: morbidity (including maternal and fetal), mortality (including maternal and fetal), time to transfusion, alloimmunization, HTRs, recurrence or progression of primary indication for chronic transfusion, intensive care unit (ICU) admission, ventilator support, postoperative acute chest syndrome, iron overload, iron-induced liver disease/failure, iron-induced cardiac disease, and iron-induced endocrinopathies. Outcomes for each question are described in Table 2.

Table 2. Outcomes for each prioritized question

	Critical outcomes for decision-making
Q1.	• Time to transfusion (delay to treatment) • Time to antibody identification • Alloimmunization • HTR • Mortality • Morbidity
Q2.	• HTR • Alloimmunization rate • Alloimmunization prevalence • Morbidity • Mortality
Q3.	• Alloimmunization • HTR • ICU admission • Mortality • Infection • Pain • Adverse effects (aseptic meningitis, avascular necrosis [AVN])
Q4.	• Length of stay • Morbidity (stroke, renal function) • Mortality • Infection (meningococcemia, hepatitis B reactivation) • Pain • Adverse effects (aseptic meningitis, AVN)
Q5.	• Alloimmunization • RBC unit use • Frequency of visits • Iron overload • HbS suppression • Recurrence or progression of primary indication for chronic transfusion (stroke, acute chest syndrome, pain) • Adverse reactions (fever, allergic, procedural such as nausea, citrate toxicity, hypotension, presyncope) • Line-related complications • Duration of procedure
Q6.	• Length of hospital stay • Length of ICU stay • Ventilator support (days) • Morbidity (during hospital stay) • Mortality • HbS level • Alloimmunization • Adverse reactions (fever, allergic, fluid overload, procedural such as nausea, citrate toxicity, thrombocytopenia) • Line-related complication
Q7.	• RBC unit use • Frequency of procedures • Iron overload • HbS suppression
Q8.	• Alloimmunization • Maternal mortality • Vaso-occlusive pain episodes • Pulmonary complications • Pulmonary embolism • Pyelonephritis • Perinatal mortality • Small size for gestational age/low birth weight • Neonatal death • Preterm birth
Q9.	• Postoperative acute chest syndrome • Postoperative pain crisis • All other postoperative complications (infection, thrombosis) • Mortality • Alloimmunization • Adverse reactions (allergic, fever) • Length of stay
Q10.	• Iron-induced liver disease/failure • Iron-induced cardiac disease • Iron-induced endocrinopathies (growth failure, delayed puberty, hypothyroidism, diabetes) • Mortality

Evidence review and development of recommendations

The Mayo Program identified published studies for each guideline question, using the search strategies described in supplemental File 4. For each guideline question, the Mayo Program then prepared a GRADE summary of findings table and a GRADE EtD framework, using the GRADEpro Guideline Development Tool (https://gradepro.org/).[5,6,11] The summary of findings tables summarize for 1 PICO (population, intervention, comparison, outcomes) at a time the evidence for each of its critical outcomes and the rating of the certainty of that evidence. The EtD table summarizes the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addresses effects of interventions, resource use (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure the inclusion of recent studies, panel members were asked to suggest any studies that might be eligible but were not included in the summary of findings tables.

Under the direction of the Mayo Program, researchers followed the general methods outlined in the Cochrane Handbook for Systematic

Reviews of Interventions (https://training.cochrane.org/handbook) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk for bias were either randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk for bias was assessed at the health outcome level using the Cochrane Collaboration's risk for bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD frameworks.[5,6,11] Subsequently, the certainty of the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach, based on the following domains: risk for bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk for publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual and opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[7-9]

During a 2-day in-person meeting followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty of the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. The approach is described in detail in Murad et al.[14]

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional," according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. Table 3 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, healthcare policy makers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 20 August 2018 for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Forty-seven individuals, 2 organizations, and 2 companies submitted comments. The panel revised the document to address pertinent comments, but that resulted in no changes to the recommendations. The guidelines were reviewed by the ASH Guideline Oversight Subcommittee on 27 September 2019. On 21 October 2019, the ASH Committee on Quality confirmed that the defined guideline development process was followed, and on 25 October 2019, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, and availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by forthcoming decision aids.

Recommendations

Red cell antigen profiling

Should an extended red cell antigen profile be obtained by genotype or serology vs only ABO/RhD type for patients with SCD?

Recommendation 1

The ASH guideline panel *suggests* obtaining an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before first transfusion) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- An extended red cell antigen profile includes C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, S/s at a minimum.
- Red cell antigen profiles should be made available across hospital systems.
- A serologic phenotype may be inaccurate if the patient has been transfused in the past 3 months.
- Genotyping is preferred over serologic phenotyping, as it provides additional antigen information and provides increased accuracy for, among other things, C antigen determination and Fy^b antigen matching.

Table 3. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; you must help each patient arrive at a management decision consistent with patients' values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Specific background. Routine transfusion therapy includes typing for ABO and RhD, but for patients with SCD, prevention of alloimmunization requires additional blood group antigen information. When the extended red cell antigen phenotype is obtained, the extent of antigen typing and whether serologic or molecular methods are used vary among institutions. The effect of only ABO/RhD typing compared with an extended red cell antigen phenotype on time to transfusion and time to antibody identification is not well documented in the existing literature and is highly variable based on the experience of the laboratory and the complexity of the serologic presentation. Red cell genotyping provides more comprehensive information by including antigens for which there are no serologic reagents and improves accuracy for certain antigens, such as C determination and matching for Fy^b, but the effect on transfusion outcomes has not been reported.

Summary of the evidence. The systematic review identified a single comparative observational study (total, 35 patients).[20] Outcomes that the guideline panel considered important to patients were (1) time to transfusion and (2) time to antibody identification. There were no studies that compared the outcomes of only ABO/RhD typing to an extended blood group antigen profile. The paucity of studies on this topic reflects what is considered "common knowledge" in the profession regarding the pretransfusion testing process (ie, having an extended red cell antigen profile for a patient who presents with a positive antibody screen and incompatible crossmatches expedites identification of the cause of the incompatibility and aids selection of compatible donor units). Outcomes are difficult to measure, as they vary considerably depending on the specificity of the antibody in the patient plasma, the complexity of the patient's transfusion complications, the level of expertise in the testing laboratory, and the availability of donor units in a hospital inventory.

Benefits. The panel judged the desirable effects of extended red cell antigen profiling relative to ABO/RhD typing to be moderate. An extended red cell antigen profile may benefit patients who develop a positive antibody screen or experience an acute or delayed transfusion reaction by facilitating antibody identification and making it possible to find compatible blood. Red cell typing for Rh (C/c, E/e) and K antigens is necessary to implement Rh and K antigen matching (Recommendation 2), which reduces alloimmunization. More extended antigen profiles to include Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s can expedite antibody identification and donor unit selection when a patient requiring transfusion presents with a positive antibody screen.

Harms and burden. The panel judged the undesirable effects of extended red cell antigen profiling relative to ABO/RhD typing to be trivial. Because many patients with SCD develop a positive antibody screen, performing ABO/RhD typing alone carries an increased risk for harm from delays in antibody identification and finding compatible donor units. Transfusion delays can negatively affect the health of patients and can be costly. In general, the risk for adverse events associated with performing an extended red cell antigen profile were negligible, but cost is a consideration.

Special methodological considerations. DNA-based red cell antigen typing can overcome certain limitations of serologic assays, such as recent transfusion or interfering allo- or autoantibodies. Molecular genotyping also carries a lower risk for error than serologic typing.[21] Many blood group genotyping assays have been developed and may include up to ~40 antigens. Genotyping also provides improved accuracy for C and Fy^b antigen matching. Although genotyping is preferred over the serologic phenotype, the panel acknowledges that for most hospital transfusion services, it is a referral test that lengthens the turnaround time and thus supports testing at first encounter. Genotyping is available at many blood centers and is being used to type blood donors, which may facilitate economical testing for patients.

Rationale and key driver for recommendation. The key drivers of the recommendation are expert opinion and long-standing laboratory experience (supplemental File 5). It is well-recognized that the most common antibodies complicating transfusion for patients with SCD are directed against C, E, and K antigens.[22-24] It is intuitive that avoiding the most common antigenic incompatibilities when transfusing patients avoids

immunization. Despite efforts to avoid sensitization to these antigens, alloimmunization still occurs, although with lower frequency. Patients receiving matching protocols for Rh (C, E or C/c, E/e) and K antigens can present with positive antibody test results as a result of incompatibility for any number of additional clinically significant antigens or inheritance of altered Rh antigens with or without apparent autoantibody production. These can be complex and difficult to resolve. Laboratory experience indicates that having additional patient antigen information expedites compatibility workup and aids selection of compatible donor units.

Other EtD criteria and considerations. The panel judged the resources required for antigen matching as moderate. Donor units with extended antigen typing are associated with increased costs from the blood center. Historically, providing donor units typed for more than ABO/RhD has involved labor-intensive manual serologic methods reflected in the cost structure. Importantly, with the introduction of genotyping, extended antigen typing of donors is becoming more economical and accessible. Cost recovery is currently a challenge in the absence of direct reimbursement for prophylactic prevention of alloimmunization and, therefore, must take the form of reduced hospital labor and reagent and testing costs and improved turnaround time and patient care. Minority blood donor recruitment efforts are crucial, and the expert panel encourages centers that treat patients with SCD to establish a close partnership with the blood provider.

Technical remarks. The extended red cell antigen profile, by serology or genotype, needs be performed only once and made part of the patient medical record. The result should be shared between health providers. Testing should be performed on the first encounter, especially if performed by serologic typing, as serologic testing on red cells other than a pretransfusion sample carries a significant risk for error. Serologic red cell typing can be performed for those who have not been transfused in the preceding 3 months and do not have a positive direct antiglobulin test. Serologic typing is a straightforward assay with a short turnaround time for hospitals who have reagents available.

Conclusions and research needs for this recommendation. The systematic review found no published evidence for a net health benefit from obtaining an extended red cell antigen profile on patients with SCD, but expert opinion and experience suggest it informs transfusion therapy when interpreting complex antibody evaluations and reduces alloimmunization when used to antigen-match patients with blood donors. The guideline panel identified the following additional areas of research that are needed: (1) prospective studies to determine the effect on transfusion outcomes when an extended blood group antigen profile is obtained for patients with SCD at the first encounter and (2) prospective, randomized studies to determine the effect on transfusion outcomes when a red cell profile is obtained by molecular vs serologic methods.

Prophylactic red cell antigen matching for transfusion

Should prophylactic Rh (C, E, or C/c, E/e)- and K-matched red cells or prophylactic Rh (C, E or C/c, E/e)-matched, K-matched, and extended matched (Jk^a/Jk^b, Fy^a/Fy^b, S/s) red cells, by serologic or genotype-predicted red cell antigen profile, vs only ABO/RhD-matched red cells be used for patients with SCD receiving transfusions?

Recommendation 2

The ASH guideline panel *recommends* prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks:

- The extended red cell antigen profile may be determined by genotype or serology.
- Extended red cell antigen matching (Jk^a/Jk^b, Fy^a/Fy^b, S/s) may provide further protection from alloimmunization.
- Patients who have a GATA mutation in the *ACKR1* gene, which encodes Fy antigens, are not at risk for anti-Fy^b and do not require Fy^b-negative red cells.
- Patients identified by genotype with the hybrid *RHD*DIIIa-CE (4-7)-D* or *RHCE*CeRN* alleles, which encode partial C antigen, and no conventional *RHCE*Ce* or **CE* allele should be transfused with C-negative red cells to prevent allo-anti-C development.

Specific background. Red cell alloimmunization incidence in patients with SCD is the highest of any transfused patient population, for reasons that remain poorly understood.[22,25] Relatively large transfusion burdens, in combination with the inflammatory component of SCD and its complications, play a role.[26,27] *RH* genetic diversity in patients with SCD is an additional risk factor, with the majority having at least 1 *RH* allele that differs from those found in individuals of European descent.[24,28] Antibodies to Rh (D, C/c, E/e) and K have historically been the most common specificities identified in patients with SCD.[22-24] In addition to making it difficult and, at times, impossible to locate compatible red cell units, alloantibodies to these and other blood group antigens can result in clinically significant hemolysis in both transfusion and pregnancy settings. The presence of such antibodies significantly increases the risk for acute or delayed HTRs that may be associated with bystander hemolysis and hemolytic disease of the fetus and newborn. Thus, preventing red cell alloimmunization altogether or decreasing the number of red cell alloantibodies formed is a desirable goal. The optimal degree of antigen matching for patients with SCD remains unclear, given the resources required for antigen matching compared with the potential morbidity and mortality associated with red cell alloantibody formation.

Summary of the evidence. The systematic review identified 28 studies (total, 2535 patients). These were 4 randomized controlled trials (RCTs), 7 comparative observational studies, and 17 non-comparative observational studies. Studies were examined for the following outcomes: alloimmunization incidence rate (new antibodies formed per number of transfused units), alloimmunization prevalence (number of patients alloimmunized), HTRs, morbidity, and mortality. The panel identified only 2 observational studies that directly compared the incidence rate of new alloantibody formation in patients with SCD transfused with either phenotypically matched red cells (Rh and K matched or extended matched) or ABO/RhD-matched red cells.[29,30] One of these studies compared both Rh (C/c, E/e)- and

K-matched and extended matched red cell transfusions with ABO/RhD-matched red cell transfusions and reported an incidence rate for new red cell alloantibodies per 100 transfused red cell units of 0.9 for Rh- and K-matched red cells compared with 3.1 for ABO/RhD-matched red cells.[29] The other study compared Rh (C/c, E/e)- and K-matched red cells with ABO/RhD-matched red cells and reported an incidence rate for new red cell alloantibodies per 100 transfused red cell units of 0.053 for Rh- and K-matched red cells and 0.189 for ABO/RhD-matched red cells.[30] Therefore, in terms of the incidence rate of new alloantibody formation in patients with SCD, these 2 studies demonstrate a clear benefit of providing Rh- and K-matched red cells over only ABO/RhD-matched red cells.

In addition to the 2 primary observational comparator studies, there were many single-group studies identified that described alloimmunization prevalence with or without alloimmunization incidence rates per number of units transfused in patients with SCD. These studies were cross-sectional, and there was significant heterogeneity between patient groups among the studies, including the age and unit exposure history of the patient, the method of transfusion (simple vs RCE), and the indication for transfusion. When reported alloimmunization prevalence data were pooled, statistically significant differences were observed between patient populations receiving extended phenotypically matched red cells (pooled alloimmunization prevalence, 8%; 95% confidence interval [CI], 2%-18%; n = 5)[31-35] and those receiving ABO/RhD-matched red cells (pooled alloimmunization prevalence, 35%; 95% CI, 19%-53%; n = 5).[29,30,36-38] No statistically significant differences in red cell alloimmunization prevalence were observed between SCD patient populations receiving Rh (C, E or C/c, E/e)- and K-matched red cells (pooled alloimmunization prevalence rate, 18%; 95% CI, 10%-27%; n = 15)[24,30,36-46] and those receiving ABO/RhD-matched red cells, or between those receiving extended phenotypically matched red cells and those receiving Rh (C, E or C/c, E/e)- and K-matched red cells.

Importantly, the incidence rate of alloimmunization per 100 red cell units transfused was determined, as this minimizes bias of transfusion burden among different studies. In brief, 9 studies reported an alloimmunization incidence rate of 0.40 (95% CI, 0.23-0.69) new alloantibodies per 100 units transfused of Rh (C, E or C/c, E/e)- and K-matched red cells.[24,30,38,41,46-50] Five studies reported an incidence rate of 0.25 (95% CI, 0.09-0.71) new alloantibodies per 100 units transfused of extended matched red cells.[31,33-35,51] Six studies reported an incidence rate of 1.94 (95% CI, 1.28-2.94) per 100 units transfused of ABO/RhD-matched red cells.[23,29-31,38,52] When the data were combined, any extent of matching (Rh [C, E or C/c, E/e] and K, as well as extended matching) resulted in a significantly lower incidence rate of red cell alloantibodies per 100 red cell units transfused compared with ABO/RhD matching alone.

Benefits. The panel judged as moderate the desirable effects of prophylactic matching Rh (C, E or C/c, E/e) and K antigens relative to ABO/RhD alone. The primary outcome evaluated in all identified studies was red cell alloantibody formation. Although multiple studies have described alloimmunization prevalence or incidence rates, there is a lack of studies with direct comparison of matching Rh (C, E or C/c, E/e) and K antigens to ABO/RhD alone. However, comparison of alloimmunization incidence rate per number of units transfused between recipients of matched red cells (Rh [C, E or C/c, E/e] and K or extended) vs ABO/RhD-matched red cells documents the benefit of fewer new red cell alloantibodies detected after Rh- and K-matched red cell transfusions. The certainty of this evidence by GRADE criteria was judged as moderate. Of note, no studies addressed the benefits of prophylactic antigen-matching transfusion protocols on subsequent risk for relevant clinical outcomes in patients with SCD, such as prevention of acute or delayed HTRs or mortality.

Harms and burden. The panel judged as trivial the undesirable effects of prophylactic matching Rh (C, E or C/c, E/e) and K antigens relative to ABO/RhD alone. The relative effects of potential harms and burdens were not evaluable because of the lack of published data. Potential harms of Rh (C, E or C/c, E/e)- and K-matched red cell transfusions may be related to transfusion delays if identification of antigen-negative units is difficult; this may occur when an alloimmunized patient requires red cell units that are negative for multiple antigens. Expense and resource use are also considerations, as are the risks for adverse outcomes of red cell alloantibodies in transfusion and pregnancy settings, both short and long term.

Rationale and key driver for recommendation. The balance of benefits vs harms favors prophylactic red cell matching for Rh (C, E or C/c, E/e) and K antigens or extended antigens (Jk^a/Jk^b, Fy^a/Fy^b, S/s) over ABO/RhD alone, based primarily on the alloimmunization incidence rate reduction using these matching protocols (supplemental File 5). By preventing alloantibody formation, subsequent acute and delayed HTRs, difficulty in identifying sufficient antigen-negative red cell units, and transfusion delays can also be avoided. Although the certainty of evidence by GRADE criteria was moderate because RCTs directly comparing antigen-matching strategies have not been performed, the guideline panel issued a strong recommendation in favor of reduced alloimmunization incidence rate with any extent of matching beyond ABO/RhD.

Other EtD criteria and considerations. This recommendation focuses on Rh (C, E or C/c, E/e) and K matching, or more extended matching between blood donors and transfusion recipients, by either serologic or genotype methods. The guideline panel acknowledges that despite serologic matching for Rh (C, E or C/c, E/e) antigens, patients with SCD remain at risk of forming alloantibodies to various epitopes within the Rh system as a result of the increased prevalence of *RH* variants in this patient population.[24] Therefore, a high index of suspicion should be maintained for the presence of *RH* variants in patients with SCD who have antibodies to Rh antigens despite exclusively receiving Rh (C, E or C/c, E/e)-matched red cell transfusions. The panel judged the resources required for prophylactic matching as moderate. The panel also valued the availability of compatible blood when needed. By avoiding alloimmunization events, there may be cost savings incurred by the ability to safely transfuse when indicated.

Conclusions and research needs for this recommendation. In spite of the lack of intervention and comparator studies, the certainty of evidence based on GRADE criteria for a net health benefit from implementing prophylactic Rh (C, E or C/c, E/e)- and K-matched or more extended matched red cell transfusion protocols for transfusion to patients with SCD was judged as moderate. However,

the evidence demonstrates lower red cell alloantibody incidence rates when any extent of red cell antigen matching beyond ABO/RhD is provided. Therefore, the panel recommends prophylactic Rh (C, E or C/c, E/e) and K antigen matching over ABO/RhD matching for patients with SCD receiving transfusions.

Further research initiatives are needed to evaluate the cost-effectiveness of various prophylactic antigen matching approaches. Given the existing literature on alloimmunization with Rh (C, E or C/c, E/e)- and K-matched red cells compared with only ABO/RhD-matched red cells, a prospective, randomized multicenter clinical trial to compare these transfusion strategies would not be feasible because of poor acceptability. The guideline panel identified the following research priorities: (1) the role of serologic vs genotypic matching, most notably for the Rh system, and (2) the development and study of universally available transfusion registries to reduce alloimmunization-related sequelae, such as delays in transfusion and DHTRs because of the high rate of multisite transfusion[53,54] and known antibody evanescence patterns.[55]

Prevention of hemolytic transfusion reactions in high-risk patients

Should immunosuppressive therapy (IVIg, steroids, and/or rituximab) vs no immunosuppressive therapy be used for patients with SCD (all genotypes) with an acute need for transfusion and a high risk for hemolytic transfusion reaction?

Recommendation 3

The ASH guideline panel *suggests* immunosuppressive therapy (IVIg, steroids, and/or rituximab) over no immunosuppressive therapy in patients with SCD (all genotypes) with an acute need for transfusion and at high risk for acute hemolytic transfusion reaction or with a history of multiple or life-threatening delayed hemolytic transfusion reactions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- These are rare clinical situations in which patients are experiencing life-threatening anemia that require immediate red cell transfusion and either compatible blood cannot be found (ie, patients with alloantibodies for whom antigen-negative blood is unavailable) and/or the patients have a history of repeated episodes of severe hemolytic transfusion reactions with or without an antibody specificity identified (even when compatible blood is available).
- The hematologist and transfusion medicine specialist should have ongoing discussions to weigh the potential benefits and harms associated with transfusion vs the effect of ongoing life-threatening anemia and to consider the respective mechanisms of action for choice of therapy (IVIg, steroids, or rituximab).
- A shared decision-making process is critical.

Specific background. Acute and delayed HTRs are among the most challenging complications of transfusion support in patients with SCD, particularly as they may have a fatal outcome.[56] Immunized patients are at risk of producing additional antibodies with further transfusion. It remains unclear whether immunosuppression benefits patients with an acute need for transfusion and at high risk for acute hemolytic transfusion reaction (AHTR). These include patients with alloantibodies for whom antigen-negative blood is unavailable and those with a history of multiple or life-threatening DHTRs. Little guidance exists on how to optimally tailor treatments based on the risk for an acute or delayed HTR and on the mechanisms responsible for red cell clearance after incompatible transfusion against different red cell antigens.

Summary of the evidence. The systematic review identified only 3 case reports and 1 case series (total, 11 patients) that addressed the use of preventative immunosuppressive therapy in patients with SCD requiring red cell transfusion but at high risk for an acute or delayed HTR. Treatment varied considerably: 2 children were treated with corticosteroids[57] and 10 individuals were treated with rituximab at different doses and timing relative to transfusion.[56,58,59] Studies examined the following outcomes: alloimmunization, HTRs, ICU admission, mortality, infection, pain, and other adverse events. After rituximab treatment, no new alloantibodies were reported in a case series of 8 patients with a follow-up period that ranged from 3 to 12 months,[58] whereas 1 patient in a case report developed new reactivity in his antibody screen without a specific alloantibody detected.[56] Mild DHTRs were reported for 3 individuals with a history of severe DHTR who received rituximab between 30 days before and 3 days after transfusion.[58] A DHTR occurred in 1 case report of a patient with a history of multiple alloantibodies and prior DHTR who was treated with rituximab 4 days before RCE with 5 red cell units.[59] Of 2 patients with prior DHTRs who were treated with corticosteroids at the time of the next transfusion, 1 experienced another DHTR.[57] Among patients treated with rituximab (n = 10), 2 required an ICU admission,[56,58] 1 died with the last tested hemoglobin of 2 g/dL,[56] 3 experienced posttransfusion vaso-occlusive pain, and 3 experienced hemoglobinuria.

Benefits. The panel was not able to provide a judgment about the size of benefits. There were no direct, comparative studies of patients at risk for acute or delayed HTR treated with immunosuppression vs no immunosuppression. Although the evidence suggests that immunosuppression does not prevent all subsequent HTRs in at-risk patients, a potential benefit of immunosuppression for patient outcomes is suggested by the high-risk patients who did not experience a recurrent DHTR.[56-59] However, given the heterogeneity of alloantibodies and clinical scenarios, it is difficult to determine whether immunosuppression was beneficial for a given patient.

Harms and burden. The panel judged the undesirable effects as moderate. This judgment was based on very limited data. One study reported neurological sequelae that were attributed to steroid use.[57] The limited number of reports identified did not report any clear infectious risk from using immunosuppression.[59] Given the available evidence, the guideline panel suggested that special consideration might be warranted in patients with active infection. It should be noted that reports of severe pain, vaso-occlusive episodes, and even death were all attributed to the failure of immunosuppression to prevent an HTR.[56,58]

Rationale and key driver for recommendation. Given the significant morbidity and mortality associated with acute and delayed HTRs and weighed against the potential adverse effects typically experienced with rituximab, IVIg, and/or corticosteroids, the guideline panel provided a conditional recommendation in favor of immunosuppression (supplemental File 5). The panel acknowledges that the choice of therapy should be based on the patient's risk for an acute or delayed HTR and the mechanism by which red cell clearance is expected to occur for the individual at risk. For example, efforts to prevent DHTR may benefit from immunosuppression that mitigates new alloantibody production (ie, rituximab), whereas interventions aimed at inhibiting antibody-mediated hemolysis (ie, IVIg and steroids) would be predicted to be more effective in preventing a potential AHTR.

Other EtD criteria and considerations. The panel judged that prophylactic immunosuppression for patients at risk for a life-threatening HTR is probably acceptable and feasible for care providers and patients. However, given the unpredictable rate of DHTR recurrence and the unclear benefit of immunosuppression to prevent an HTR, the panel acknowledges that some clinicians may not find this approach acceptable. Differences in practice likely exist depending on the experience and overall practice preferences of individual institutions. Although variability in immunosuppressive approaches exists, the panel consensus was that supportive care, including erythropoietin with or without IV iron, should be initiated in all patients before transfusion. Transfusion with extended matched red cell units should be considered for high-risk patients, but unit availability and potential transfusion delays should also be considered. Serial monitoring of the hemoglobin, hematocrit, quantification of hemoglobin A and S fractions, reticulocyte count, bilirubin, LDH, and urinalysis (for hemoglobinuria) is advised.

A dose of 375 mg of rituximab/m^2 repeated after 2 weeks,[58] methylprednisolone or prednisone at 1 to 4 mg/kg per day, and IVIg at 0.4 to 1 g/kg per day for 3 to 5 days (up to a total dose of 2 g/kg) have been used to treat HTRs, but similar dosing would be suggested for preventative therapy as well.

Conclusions and research needs for this recommendation. The guideline panel concluded that the available data provide very low certainty evidence regarding the benefits and potential harm of immunosuppressive therapy to prevent AHTRs or DHTRs after an incompatible red cell transfusion. The panel identified the following research priorities: (1) design of tools or models for rapidly and accurately predicting the clinical relevance of alloantibodies in a given patient; (2) studies to elucidate the mechanism or mechanisms of HTRs after incompatible red cell transfusion with distinct alloantigen targets in an effort to develop more effective approaches to prevent HTRs; and (3) high-quality studies evaluating the efficacy of currently available immunomodulatory agents in preventing AHTRs or DHTRs in patients deemed at risk.

Management of severe hemolytic transfusion reactions with hyperhemolysis

Should immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) vs no immunosuppressive therapy be used for patients with SCD (all genotypes) with ongoing hyperhemolysis (defined as rapid decline of posttransfusion hemoglobin to below the pretransfusion level)?

Recommendation 4

The ASH guideline panel *suggests* immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) over no immunosuppressive therapy in patients with SCD (all genotypes) with a delayed hemolytic transfusion reaction and ongoing hyperhemolysis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- A DHTR was defined as a significant drop in hemoglobin within 21 days posttransfusion associated with 1 or more of the following: new red cell alloantibody, hemoglobinuria, accelerated HbS% increase with a concomitant fall in HbA posttransfusion, relative reticulocytopenia or reticulocytosis from baseline, significant LDH rise from baseline, and exclusion of an alternative cause.
- Hyperhemolysis is defined as a rapid hemoglobin decline to below the pretransfusion level and rapid decline of the posttransfusion HbA level.
- Immunosuppressive therapy should be initiated promptly in patients with life-threatening hemolysis.
- The hematologist and transfusion medicine specialist should discuss potential benefits and harms associated with specific immunosuppressive therapies.
- First-line immunosuppressive agents include IVIg and high-dose steroids; the second-line agent is eculizumab. Rituximab is primarily indicated for potential prevention of additional alloantibody formation in patients who may require further transfusion.
- Depending on the length of steroid therapy, weaning to avoid precipitation of a vaso-occlusive episode should be considered.
- Avoidance of further transfusion is recommended unless patients are experiencing life-threatening anemia with ongoing hemolysis. If transfusion is warranted, extended matched red cells (C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, S/s) should be considered.
- Supportive care should be initiated in all patients, including erythropoietin with or without IV iron.
- A shared decision-making process is critical.

Specific background. In patients with SCD, HTRs can be accompanied by hyperhemolysis, defined as severe hemolysis causing the hemoglobin to drop below pretransfusion levels, suggesting clearance of the patient's own red cells in addition to transfused cells.[60-62] Hyperhemolysis can occur with no identifiable antibody and a negative direct antiglobulin test.[63] However, recognition is critical, as additional transfusions should be avoided if possible, as the hemolysis may worsen and potentially induce multiorgan failure and death.[56,64] For patients experiencing life-threatening anemia, transfusion with extended matched red cells that also lack the offending antigen should be considered. IVIg, high-dose steroids, eculizumab, and/or rituximab have been used to treat hyperhemolysis in patients with SCD, but the optimal management remains unclear.

Summary of the evidence. DHTRs with hyperhemolysis are rare events. The systematic review identified only 2 comparative studies and 23 case reports or series (total, 137 patients). There were no RCTs that compared outcomes of immunosuppressive therapy vs supportive care only in patients with SCD experiencing a DHTR, with or without accompanying hyperhemolysis. The reports were examined for the following outcomes, which the guideline panel considered to be important to patients: length of stay, mortality, changes in hemoglobin values, and adverse events. None of the studies reported on morbidity (eg, stroke or changes in renal function), infection risk, and pain. Twenty case reports and series that included 36 patients reported an improvement in hemoglobin values after treatment with IVIg, high-dose steroids, eculizumab, and/or rituximab.[59,61,65-79] Regarding mortality, 1 retrospective study compared 53 patients who received supportive care only with 46 patients who received an immunosuppressive regimen and found 3 deaths in each group.[80] Another retrospective study examined 23 DHTR episodes, with 4 episodes managed by supportive care alone, 5 with immunosuppression with or without additional red cell transfusion, and 14 with red cell transfusion alone. Among these, 1 patient who received transfusion alone and 1 who received both immunosuppression and transfusion died.[64] No adverse events after treatment with rituximab and methylprednisolone were reported by 2 studies with 4 patients.[59,68]

Benefits, harms, and burden. The panel was not able to provide a judgment about the size of benefits and judged the undesirable effects as moderate. Several case reports and case series did show a correlation between initiation of immunosuppressive therapy and rises in hemoglobin values.[59,61,65-79] However, the panel acknowledged the potential for selection bias in published results.

Rationale and key driver for recommendation. The potential harm of not providing immunosuppressive therapy to an individual experiencing a DHTR with ongoing hyperhemolysis is possible, but unpredictable. Considering both the potential reduction in morbidity and mortality and the possible adverse effects experienced with IVIg, corticosteroids, eculizumab, and rituximab, the guideline panel suggests immunosuppressive therapy for patients with SCD experiencing hyperhemolysis (supplemental File 5). The panel judged that the potential benefit of reducing sequelae of ongoing hemolysis, severe anemia, and risk for subsequent DHTR if transfused for life-threatening anemia outweigh the risks associated with immunosuppression.

Other EtD criteria and considerations. Differences in practice and choice of immunosuppressive agents are likely to exist depending on the experience of individual institutions. For all patients experiencing a life-threatening DHTR with accompanying hyperhemolysis, supportive care including erythropoietin with or without IV iron should be initiated. Serial monitoring of the hemoglobin, hematocrit, quantification of HbA and HbS fractions, reticulocyte count, bilirubin, LDH, and urinalysis (for hemoglobinuria) is also advised. The mechanism of antibody-induced red cell clearance by the implicated alloantibody should be considered for individual patients. Discussion between the hematologist and transfusion medicine specialist is advised to determine the optimal approach for each patient. Based on case reports and expert consensus, high-dose steroids and IVIg are considered first-line treatment, followed by eculizumab for patients who continue to experience clinical deterioration despite first-line agents. Methylprednisolone or prednisone at 1 to 4 mg/kg per day and IVIg at 0.4 to 1 g/kg per day for 3 to 5 days (up to a total dose of 2 g/kg) have been used.[79,81,82] For eculizumab, adult patients (>40 kg) have been given 900 to 1200 mg weekly for hyperhemolysis (refer to prescribing guidelines for patients with a weight of <40 kg).[72,83] When considering eculizumab, immediate vaccination with Menveo (MenACWY), either Bexsero or Trumenba (MenB), and ciprofloxacin prophylaxis are advised to reduce the risk for meningococcal infection. If a patient is experiencing life-threatening anemia, transfusion should not be withheld, and if feasible, extended antigen-matched red cells (C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, S/s) should be transfused. Rituximab is primarily indicated for potential prevention of additional alloantibody formation in patients who may require further transfusion.

For DHTRs lacking an identifiable antibody specificity, the panel suggests serial antibody screening within 3 months of the DHTR for detecting new antibodies. The antibody specificity may become apparent weeks to months after a DHTR event, and can inform antigen-negative unit selection for future transfusions.

Conclusions and research needs for this recommendation. Because DHTRs with hyperhemolysis are uncommon, it would be difficult to design RCTs to determine the optimal treatment. The panel identified the following research priorities: (1) high-quality studies to determine the efficacy of immunomodulatory agents (IVIg, steroids, eculizumab, and rituximab) for the treatment or prevention of hemolytic transfusion reactions, with or without hyperhemolysis; (2) studies on the mechanisms and consequences of alloantibody-mediated clearance of transfused red cells and the pathophysiology of hyperhemolysis; and (3) studies of interventions to prevent the deleterious consequences of hemolysis itself, such as the use of plasma-derived haptoglobin and hemopexin in patients with excessive hemolysis.

Transfusion modality in patients with SCD requiring chronic therapy

Should automated RCE vs simple transfusion or manual RCE be used for patients with SCD receiving chronic transfusions?

Recommendation 5

The ASH guideline panel *suggests* using automated RCE over simple transfusion or manual RCE in patients with SCD (all genotypes) receiving chronic transfusions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The decision-making process should consider the clinical indication, baseline and target total hemoglobin and HbS%, patient age, patient preferences (particularly if central venous access is needed), iron overload status and iron chelation compliance, feasibility, and availability of compatible red cells.

Specific background. A major goal for chronic red cell transfusion therapy is to maintain the HbS% below a target threshold to

reduce SCD-related complications, most notably for stroke prevention.[84] The 3 primary methods are automated RCE, manual RCE, and simple transfusion. Simple transfusion can be performed with peripheral venous access and requires the fewest red cell units. However, simple transfusion can lead to hyperviscosity and circulatory overload, and iron loading is inevitable. Manual RCE requires trained personnel, more red cell units than simple transfusion, and possibly central line placement. Although manual RCE can achieve isovolemia, blood removal and replacement occur sequentially, so blood volume shifts can be minimized. Manual RCE procedures typically require more time than automated RCE. Automated RCE requires a specialized apheresis device and specially trained nurses, and more commonly requires an indwelling central line. With automated RCE, the target HbS%, hematocrit, and overall fluid balance can be precisely programmed. Blood removal is continuous with saline or red cell replacement, which also minimizes acute blood volume shifts.

Summary of the evidence. The systematic review identified 14 comparative observational studies (total, 652 patients). Nine studies compared automated RCE with simple transfusion (average patient ages in the studies, 7.3-20 years),[85-93] and 6 studies compared automated RCE with manual RCE (average patient ages in the studies, 5.9-27 years).[87,94-98] Most patients were of the SS genotype.

Compared with simple transfusion, automated RCE was associated with increased red cell unit requirement,[88,89] but was not associated with increased alloimmunization or adverse transfusion reactions.[85-88,90,93] Automated RCE was associated with lower levels of iron overload, with a mean difference between the 2 methods of ferritin change ranging from −106 (95% CI, −153 to −59) to −21.7 (95% CI, −27.8 to −15.6) ng/mL per month.[87,91] The mean difference in liver iron stores was −7.0 (95% CI, −9.2 to −4.8) mg/g [dw] per year.[87,99] Only 1 study assessed frequency of procedures and HbS suppression and found no difference between those receiving automated RCE and those receiving simple transfusion.[87] The certainty of evidence was judged to be very low because of imprecision, inconsistency, and/or high risk for bias.

Compared with manual RCE, 3 studies reported increased red cell unit use with automated RCE,[95,98,100] whereas 1 study reported a slight decrease in red cell unit use.[97] Automated RCE increased the odds of achieving the desired preprocedure HbS suppression (odds ratio [OR], 5.5; 95% CI, 1.07-28.22),[87,95,98] with shorter procedure duration (average of 91 and 115 minutes vs 150 and 257 minutes)[95,96,98] and increased intervals between procedures (average of 30 and 47 days vs 28 and 35 days).[87,95,97,98] Only 1 study compared new alloimmunization in patients receiving automated vs manual RCE and found increased odds with automated RCE (OR, 2.5; 95% CI, 0.07-58.66).[87] Three studies reported no significant difference in ferritin levels between automated and manual RCE,[87,94,97] but 1 study found lower liver iron stores with automated RCE than manual RCE with chelation (difference of −8.00 mg/g [dw] per year).[87]

Benefits, harms, and burden. The panel judged the desirable effects as moderate. Although the certainty of evidence is very low, the primary potential benefit of automated RCE compared with manual RCE or simple transfusion is decreased iron overload. Automated RCE was not associated with increased risk for adverse effects (red cell alloimmunization and adverse procedural reactions), although line-related complications were not consistently assessed or reported. Red cell unit use is increased with automated RCE, and identifying sufficient compatible units may be burdensome. Compared with manual RCE, automated RCE is believed to have less burden because of reduced procedure duration and frequency and improved HbS suppression compared with manual exchange.

Rationale and key driver for recommendation. Despite the very low certainty of evidence, the panel suggests automated RCE over manual RCE or simple transfusion for patients with SCD requiring chronic transfusions (supplemental File 5). Compared with simple transfusion, the primary potential benefit is the reduced iron overload. Compared with manual RCE, the main benefits are improved HbS suppression, reduced procedure time, and reduced procedure frequency with no significant evidence of increased risks.

Other EtD criteria and considerations. Automated RCE requires specialized apheresis devices, which require maintenance and trained personnel. Although this service can be outsourced, it is still a significant investment of resources. Cost may be regained through savings in hospitalizations, iron chelation therapy, and for manual exchange, personnel time required. For highly immunized patients requiring red cells lacking multiple or high-prevalence antigens, automated RCE may not be feasible.

Automated RCE may be particularly useful to prevent or reduce iron overload in patients who cannot tolerate, have adverse effects from, or are noncompliant with chelation therapy. In the absence of iron chelation, neutral or negative iron balance is achieved by targeting an end hematocrit that is equal to or lower than the starting hematocrit. The number of units exchanged to reach the target end hematocrit and HbS% goals should be guided by pre- and postprocedure hemoglobin fractionations and hematocrits. Net red cell gain with each procedure can also be calculated as follows: patient total blood volume × (postprocedure hematocrit − preprocedure hematocrit). If preprocedure HbS% targets are unmet, the target end hematocrit may be increased or the target end HbS% decreased. If central venous access is necessary (peripheral access is preferable), the catheter should be validated for apheresis use and anticoagulated per manufacturer instructions. Apheresis device procedures require a minimum total blood volume, and in patients with a small total blood volume, a prime with red cells or albumin should be performed (typically, for patients <30 kg). Isovolemic hemodilution (Recommendation 7) is a potential option to reduce red cell unit requirements with automated RCE.

Conclusions and research needs for this recommendation. Although the recommendation is based on very low certainty of evidence, the guideline panel found a net health benefit provided with automated RCE and suggests automated RCE over manual RCE or simple transfusion in patients with SCD requiring chronic transfusion. Automated RCE likely reduces the risk for iron overload and increases the probability of achieving the desired preprocedure HbS suppression without increasing

patient harms or burdens, even with increased red cell unit requirements. Burden may be decreased through shortened procedure duration and frequency. The panel identified the following research priorities: (1) optimal peripheral access techniques (eg, ultrasound guidance) and central venous access devices and techniques for maintaining patency and sterility; (2) individualized strategies (eg, based on reticulocyte count, target hematocrit, and target HbS%) to minimize endogenous erythropoiesis, iron loading, and progression of SCD-related complications; and (3) novel RCE techniques to reduce red cell unit usage and procedure frequency.

Transfusion for patients with SCD and acute chest syndrome

Should automated or manual RCE be used over simple transfusion for patients with SCD and severe acute chest syndrome?

Recommendation 6a

The ASH guideline panel *suggests* automated RCE or manual RCE over simple transfusions in patients with SCD and severe acute chest syndrome (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Automated RCE is preferred over manual RCE to more rapidly reduce HbS levels.
- Special equipment and trained staff are needed for automated RCE.
- Patients with small total blood volumes require a red cell prime because of the extracorporeal volume of the apheresis machine.
- A pre- and postprocedure complete blood count and hemoglobin fractionation should be obtained to maximize procedure safety and efficacy.

Recommendation 6b

The ASH guideline panel suggests automated RCE, manual RCE, or simple transfusions in patients with SCD and moderate acute chest syndrome (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- There is insufficient evidence to support automated RCE or manual RCE over simple transfusions in patients with SCD and moderate ACS.
- Automated or manual RCE should be considered for patients with rapidly progressive ACS, who do not respond to initial treatment with simple transfusion, or with high pretransfusion hemoglobin levels that preclude simple transfusion.
- Automated RCE can reduce HbS levels more rapidly than manual RCE.

Specific background. ACS is one of the leading causes of death in patients with SCD,[101,102] and therefore, early recognition and treatment are crucial. The clinical spectrum of ACS is variable, and although there are no specific markers of disease severity, a significant decline in the hemoglobin concentration and/or oxygen saturations ($SpO_2 \leq 94\%$ or several percentage points below the patient's baseline) can suggest severe disease. Interventions may include antibiotics, oxygen, invasive and noninvasive respiratory support, bronchodilators, nitric oxide, and corticosteroids. The benefit of red cell transfusion for ACS has been described in case series and observational studies, but whether simple or exchange transfusion results in improved patient outcomes is unclear. Often, patients with milder degrees of hypoxia receive simple transfusions if their hemoglobin levels are low enough, whereas RCE is commonly reserved for more severe cases of ACS (ie, rapidly falling hemoglobin concentration, severe hypoxia, or requirement for invasive respiratory support).

Summary of the evidence. The systematic review identified 3 comparative observational studies (total, 157 patients) reporting on the outcomes of patients with SCD treated with RCE or simple transfusion.[103-105] Altogether, the studies examined 161 episodes of ACS, of which 40 occurred in adults and 121 in children. One noncomparative observational study of 671 ACS episodes in 538 patients was included for specific outcomes after transfusion as indirect evidence (124 patients received RCE, 238 received simple transfusion).[106] Studies were examined for the following outcomes: mortality, morbidity, length of ventilator support, alloimmunization, line-related complications, length of ICU stay, length of hospital stay, adverse reactions (such as transfusion reaction and citrate toxicity), and HbS level.

None of the studies reported on morbidity, mortality, length of ventilator support, central line complications, or HbS suppression. One study found that the RCE group spent significantly more time on oxygen than the simple transfusion group (mean, 3.7 vs 2.4 days), and 1 patient who received RCE required bilevel positive airway pressure therapy vs none with simple transfusion.[104] Indirect evidence from 1 large cross-sectional study found similar improvements in oxygenation between patients who received RCE and those receiving simple transfusion.[106] A meta-analysis of 2 studies found no significant difference in the length of hospital stay for patients treated with RCE vs simple transfusion (mean difference, 0.26 days; 95% CI, −1.17 to 1.7 days; $P = .9$).[104,105] However, the certainty of evidence was very low because of both imprecision and a high risk for bias. Patients with a more severe presentation were likely to receive more aggressive therapy at the physician's discretion. There was no evidence of difference in alloimmunization rate[104] or other adverse reactions of transfusion between the 2 groups.[103] Central line complications and HbS suppression were not examined in any of the studies.

Benefits, harms, and burden. The relative benefits, harms, and burdens were difficult to estimate because of lack of direct comparison between RCE and simple transfusion for SCD and ACS. The panel judged the degree of desirable effects to vary. The degree of the desirable effects of RCE is

likely proportional to the severity of ACS, in that patients with more severe ACS may potentially benefit from RCE by a more significant decrease in HbS% than is achieved with simple transfusion.

The potential undesirable effects were also difficult to determine because of a paucity of comparative data on alloimmunization, line-related complications, and adverse reactions to the blood product or transfusion procedure itself. The guideline panel considered the degree of undesirable effects to be small.

Rationale and key driver for recommendation. Despite the paucity of evidence, the guideline panel suggests RCE over simple transfusion in cases of severe and/or rapidly progressive ACS, given the known risk for morbidity and mortality weighed against minimal to moderate potential adverse events associated with RCE. For moderate cases of ACS, the panel suggests either RCE or simple transfusion as an acceptable treatment modality (supplemental File 5).

Other EtD criteria and considerations. The guideline panel suggests stratifying treatment by the severity of ACS, with the acknowledgment that there are no well-established definitions of severe or moderate ACS. There is also no prognostic score to identify those at highest risk for significant morbidity or mortality. For these recommendations, the guideline panel considered ACS to be severe in patients with a rapidly falling hemoglobin concentration, severe hypoxia, and/or a requirement for invasive respiratory support.

Automated and manual RCE require specialized equipment and/or trained personnel and may not be feasible in all hospital settings. For patients with severe ACS being treated at a hospital without an apheresis service, the guideline panel suggests that the treating team consider patient transfer to a center where automated RCE is available. In instances when RCE is delayed, a simple transfusion should be provided if the patient's hemoglobin level is below 9 gm/dL while waiting for RCE. Automated or manual RCE will require more red cell units than simple transfusion. In highly alloimmunized patients, identifying a sufficient number of compatible units can be difficult and may even preclude RCE.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty of evidence for a net health benefit or harm of RCE compared with simple transfusion to treat moderate or severe ACS. The evidence is hampered by few publications that included relatively few episodes of ACS mostly in children, and a high likelihood of indication bias. Thus, although no evidence of benefit from RCE was identified, this does not imply that such an effect does not exist. The guideline panel identified the following research priorities: (1) development and validation of a prognostic score and definitions of severe, moderate, and mild ACS and (2) a prospective, controlled trial of patients with severe and moderate ACS randomly assigned to treatment with RCE vs simple transfusion.

Red cell exchange with or without isovolemic hemodilution for chronically transfused patients with SCD

Should red cell exchange with IHD-RCE vs conventional RCE be used for patients with SCD receiving chronic transfusions?

Recommendation 7

The ASH guideline panel *suggests* either red cell exchange with IHD-RCE or conventional RCE in patients with SCD (all genotypes) receiving chronic transfusions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- IHD-RCE is a procedure available on some automated apheresis devices in which, before the RCE, the patient undergoes a red cell depletion with concurrent volume replacement (normal saline or 5% albumin). The intent is to decrease the number of red cell units needed for the RCE.
- Consultation with a hematologist and transfusion medicine specialist is advised to assess safety for the individual patient and technical specifications.
- IHD-RCE is not advised for acute indications for RCE or when induction of further anemia during the IHD phase may be generally detrimental (eg, recent history of stroke or transient ischemic attack, severe vasculopathy, or severe cardiopulmonary disease).

Specific background. The ASH guideline panel suggests using automated RCE over simple transfusion or manual RCE for chronically transfused patients with SCD (Recommendation 5). The 2 primary methods to perform automated RCE are the conventional method and a method that incorporates IHD before RCE. IHD-RCE, also referred to as depletion exchange, was developed to decrease the red cell unit volume needed to attain the target HbS%. The IHD-RCE technique was first described in the mid-1990s,[89] and in current apheresis devices, it is an integrally programmed procedure. With IHD-RCE, the target nadir hematocrit of the depletion phase is programmed on the device, in addition to the target hematocrit and HbS% by the end of the procedure. Although IHD-RCE maintains isovolemia, the saline or albumin replacement at the beginning of the procedure acutely lowers the hematocrit. Because acute anemic events can be a risk factor for silent or overt cerebral infarcts,[107-110] IHD-RCE is not advised for patients with significant central nervous system disease and other clinical situations in which an acute drop in the hematocrit may not be well tolerated. Of note, acute anemic events in these silent infarct studies were defined as events with a hemoglobin of 5.5 g/dL or less and more than a 30% decrease from the patient's baseline values, and in the overt stroke studies were defined as acute clinical complications with a hemoglobin level of 6.5 g/dL or less.

Summary of the evidence. The systematic review identified 5 comparative observational studies (total, 122 patients).[111-115] The reports were examined for the following outcomes, which the guideline panel considered important to patients: red cell unit use, visit frequency, iron overload, HbS suppression, recurrence or progression of primary indication for chronic transfusion, alloimmunization, adverse reactions, and procedure duration. Studies

included both pediatric and adult patients and included predominantly SS and SB^0 genotypes.

The effect of IHD-RCE on red cell unit use is unclear, with 1 study finding a decrease (IHD-RCE, 35.5 ± 4.1 mL/kg per procedure vs conventional RCE, 39.5 ± 4.6 mL/kg per procedure; $P < .0001$) translating into a mean of 1 unit,[111] but with 2 other studies finding no difference.[112,113] Procedure frequency was evaluated in 1 study that found a significant decrease (IHD-RCE interval, 7.7 ± 0.93 weeks, vs conventional RCE interval, 5.2 ± 1 weeks; $P < .0001$).[111] For iron overload, 1 study found a significant decrease in RBC unit use with IHD-RCE,[111] and 2 abstracts reported a smaller net red cell gain with IHD-RCE relative to conventional RCE.[114,115] Studies assessing HbS suppression, recurrence, or progression of the primary indication for chronic transfusion, alloimmunization, adverse reactions, and procedure duration found no significant difference between those receiving IHD-RCE and those receiving conventional RCE. The overall certainty of evidence was very low because of the risk for selection bias, the limited number of patients studied, the preliminary nature of abstracts, and the uncertain validity of outcome assessment in 1 study.[113]

Benefits, harms, and burden. The panel judged both desirable and undesirable effects to be small. The potential benefits of IHD-RCE are decreased red cell unit use, decreased RCE procedure frequency, and decreased iron overload, but the certainty of evidence was very low, in large part because of a paucity of studies and number of patients studied. The risks for harm did not appear to be increased (recurrence or progression of primary indication for chronic transfusion, red cell alloimmunization, iron overload, adverse procedural reactions). The burden associated with the procedure duration did not appear to be increased.

Rationale and key driver for recommendation. Given the very low certainty of evidence, the panel concluded that IHD-RCE cannot be recommended over conventional RCE (supplemental File 5). Limited data suggest that IHD-RCE can decrease red cell unit use, RCE procedure frequency, and iron loading, but the panel found the evidence too limited to be conclusive. Concern also remains regarding the acute decrease in hematocrit with IHD-RCE and possible predisposition to cerebral infarcts, which has not been well studied.

Other EtD criteria and considerations. Implementing IHD-RCE is feasible with current apheresis devices in which the IHD-RCE procedure is integrally programmed. Over time, there may be cost savings from decreased red cell unit use. Lower red cell use and lower net iron gain would likely increase patient equity and acceptability.

Technical remarks. IHD-RCE is not advised in clinical scenarios in which induction of further anemia may be detrimental, such as recent cerebral ischemic event, severe ACS, or severe vasculopathy. To decrease the potential risk for acute cerebral ischemic events, some empirically suggest that the IHD phase should not decrease the hematocrit to less than 21% and/or more than 20% from baseline. For patients with hypotension related to the IHD phase, 5% albumin may be considered instead of saline as the replacement fluid.

Conclusions and research needs for this recommendation. The guideline panel concluded, given the very low certainty regarding the benefits and potential harm of IHD-RCE, that either IHD-RCE or conventional RCE can be used in patients with SCD (all genotypes) receiving chronic transfusion therapy. IHD-RCE may reduce red cell use, RCE procedure frequency, and iron overload, but it may be accompanied by certain theoretical risks associated with acute anemia, such as silent cerebral infarcts. The panel identified the following research priorities: high-quality studies comparing IHD-RCE with conventional RCE in regard to red cell unit use, maintenance of the target HbS level, iron loading, safety with different indications for chronic transfusion, risk for cerebral infarcts, and cost savings.

Transfusion management during pregnancy

Should prophylactic transfusion at regular intervals vs standard care (transfusion only when indicated for a complication or exacerbated anemia) be provided to pregnant patients with SCD?

Recommendation 8

The ASH guideline panel *suggests* either prophylactic transfusion at regular intervals or standard care (transfusion when clinically indicated for a complication or hemoglobin lower than baseline) for pregnant patients with SCD (all genotypes) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- There is insufficient evidence to recommend a strategy of prophylactic transfusion rather than standard care.
- Prophylactic transfusion at regular intervals at the onset of pregnancy should be considered for women with:
  - a history of severe SCD-related complications before current pregnancy (including during previous pregnancies) to reduce recurrent pain episodes, incidence of acute chest syndrome, or other (SCD-related) comorbidities;
  - additional features of high-risk pregnancy (eg, additional comorbidities: other medical conditions or nephropathy).
- Women who develop SCD-related complications during the current pregnancy would benefit from initiating regular transfusion.

Specific background. Pregnancy in women with SCD is associated with maternal and fetal morbidity and mortality,[116,117] with the inflammatory and thrombogenic changes associated with pregnancy promoting vaso-occlusion.[118] Pregnancy is associated with a higher rate of SCD-related complications, including pain episodes, ACS, and death.[116,117,119,120] In addition, women with SCD, compared with the general population, are at increased risk for pregnancy-related complications, such as preeclampsia and miscarriage.[116,117] The rate of fetal complications, including low birth weight, small size for gestational age, and stillbirth, is also higher in pregnant women with SCD, likely because of impaired blood flow to the placenta.[116,117] This placental insufficiency is evidenced by the association between infant birth weight and placental weight,[121] as well as pathologic findings commonly seen in placentas of affected mothers, including infarcts, hemorrhage, and necrosis.[122] Although pregnancy is high risk for women with SCD and their fetuses, optimal treatment to mitigate complications has not been established. Because hydroxyurea has been demonstrated to be teratogenic in animal models

at high doses, the most commonly used strategy is scheduled red cell transfusion, but its benefits to the baby and/or the mother are unclear.

Summary of the evidence. The systematic review identified 13 studies (total, 1312 patients) of prophylactic, scheduled red cell transfusions in pregnant women with SCD. These included 12 comparative observational studies[123-134] and 1 RCT.[135] A meta-analysis was performed that examined the benefits of chronic transfusion in pregnant mothers with SCD and their fetuses, and that included the 12 observational studies. All SCD genotypes and transfusion modalities (simple and RCE) were included. Studies were examined for the following outcomes: maternal and fetal morbidity and mortality, alloimmunization, and adverse transfusion reactions.

In the only randomized trial of scheduled transfusions in pregnant women with SCD, 72 women were randomly assigned to receive scheduled or on-demand transfusions.[135] This study demonstrated reduced odds of pain episodes in the scheduled transfusion group (OR, 0.16; 95% CI, 0.05-0.51), but did not find reduced fetal complications, such as preterm birth (OR, 0.67; 95% CI, 0.19-2.34) or neonatal death (OR, 3.40; 95% CI, 0.64-18.13). Limitations of this study were that transfusions did not begin until the end the second trimester for a quarter of participants and that 44% of the nonchronic transfusion group still received on-demand transfusions for acute anemia.

The meta-analysis of observational studies demonstrated that regular transfusion for pregnant women with SCD resulted in a reduction of pain episodes (OR, 0.27; 95% CI, 0.10-0.75), pulmonary complications (OR, 0.23; 95% CI, 0.11-0.50), pulmonary embolism (OR, 0.07; 95% CI, 0.01-0.41), and maternal mortality (OR, 0.23; 95% CI, 0.06-0.91). Chronic transfusions were also found to be possibly beneficial for the fetuses of pregnant women with SCD, with lower rates of preterm birth (OR, 0.55; 95% CI, 0.34-0.88) and mortality (OR, 0.26; 95% CI, 0.07-0.93). None of the observational studies reported a difference in rate of alloimmunization.

Benefits, harms, and burden. The panel judged the benefits of prophylactic transfusions for pregnant women with SCD to be moderate. These transfusions may reduce complications by correcting severe anemia, poor oxygenation, and the degree of SCD-related vaso-occlusion in both the mother and the fetus. Studies suggest that compared with on-demand therapy, chronic transfusion may positively affect maternal and neonatal outcomes, including reduction in maternal mortality, vaso-occlusive pain episodes, and pulmonary complications, as well as neonatal death and prematurity. However, the level of certainty of the evidence is very low.

The panel judged the harms of prophylactic transfusions to be small. Little information is provided in the observational studies about potential harms of transfusion during pregnancy. These harms potentially include alloimmunization, HTRs, iron overload, and transfusion-associated circulatory overload. The single randomized trial had few alloimmunization events.[135] The meta-analysis, even with high cumulative patient numbers, was unable to examine transfusion-related complications because of the lack of reporting in the original studies and low event rates.[136]

Rationale and key driver for recommendation. To date, nearly all the studies addressing the question of scheduled transfusions for pregnant women with SCD have been observational studies, providing very low certainty of evidence. Moreover, differences in the studies regarding the mother's genotype (SS vs SC), the initiation of transfusion (first trimester or later), and the modality of transfusion (simple vs RCE) make it challenging to arrive at firm conclusions about the benefit of scheduled transfusions. On the basis of a lack of high-quality studies and limited data regarding the potential complications of transfusion in pregnancy, the guideline panel did not recommend prophylactic, scheduled transfusion over on-demand transfusion in pregnant women with SCD (supplemental File 5).

Other EtD criteria and considerations. The panel judged that implementing regular, scheduled transfusions for pregnant patients with SCD is probably feasible and acceptable. Facilities for automated RCE may not be available at all providers and may necessitate transfer of care to a center able to provide this service. Placement of a catheter via fluoroscopy, if needed, may be contraindicated, especially in the first trimester. Another risk to consider is alloimmunization with DHTRs, which could affect the mother and fetus.

Technical remarks. The guideline panel acknowledged that regular, scheduled transfusions may be appropriate for selected individuals, such as women with high-risk obstetrical features or those at high risk for SCD complications. These cases would require an assessment of the risk for complications of transfusion (iron overload, alloimmunization, and DHTRs) weighed against the potential benefit. If a decision is made to initiate regular transfusions in a pregnant woman with SCD, the guideline panel suggests a target hemoglobin level higher than 7.0 gm/dL and a peak HbS level (or S+C) of less than 50%, although it acknowledges that no evidence exists to support a specific goal for total hemoglobin level or HbS%.

Conclusions and research needs for this recommendation. The guideline panel concluded that either prophylactic transfusion at regular intervals or standard care is appropriate for pregnant patients with SCD. The panel identified the following research priorities: (1) a randomized trial of scheduled transfusions vs on-demand transfusions in pregnant women with SCD, (2) studies to determine the timing of optimal initiation of regular transfusions, and (3) studies to determine whether simple transfusion or RCE is more effective. The panel acknowledges that SCD is a rare disease and that sample size will be a challenge, thus necessitating a multicenter study.

Preoperative transfusion for patients with SCD

Should preoperative transfusion vs no preoperative transfusion be used for patients with SCD undergoing surgeries requiring general anesthesia and lasting longer than 1 hour?

Recommendation 9

The ASH guideline panel *suggests* preoperative transfusion over no preoperative transfusion in patients with SCD undergoing surgeries requiring general anesthesia and lasting longer than 1 hour (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Decision-making should be individualized according to genotype, risk level of surgery, baseline total hemoglobin, complications with prior transfusions, and disease severity.
- Clinicians should aim for total hemoglobin levels of more than 9 g/dL before surgery, and should provide RCE transfusion for patients who require preoperative transfusion but have a high hemoglobin level (>9-10 g/dL) that precludes administration of simple transfusion.

Specific background. Surgery is associated with increased mortality and morbidity in patients with SCD, particularly because of an increased risk for postoperative pain crisis and ACS. It has been postulated that treating with preoperative blood transfusion reduces the risks for postoperative complications. Some subgroups may experience more benefit from preoperative transfusion than others; for example, patients undergoing high-risk surgery (cardiac surgery or neurosurgery), patients with a low preoperative hemoglobin level (<9 g/dL), and patients with a more severe genotype (HbSS/HbSB^{0}thal) or phenotype. Similarly, there are groups of patients who may have less benefit from preoperative transfusion, eg, patients undergoing low-risk surgery, patients with a higher hemoglobin level (>10 g/dL) or HbF level, or those with a milder genotype (HbSC) or phenotype. It is also unclear whether preoperative simple transfusion (to increase preoperative hemoglobin) or exchange transfusion (to increase preoperative hemoglobin levels and reduce HbS%) is of the greatest benefit.

Summary of the evidence. The systematic review identified 14 studies (total, 1864 patients) that addressed preoperative blood transfusion for patients with SCD. These were 3 RCTs,[137-139] 7 comparative observational studies,[140-146] and 4 noncomparative observational studies.[147-150] Studies were examined for the following outcomes: mortality, postoperative ACS, pain crisis, other postoperative complications, alloimmunization, adverse reactions to blood transfusion, and length of stay. All studies included patients with SCD undergoing surgery with general anesthesia. No randomized studies were conducted in patients with genotypes other than HbSS. The panel acknowledged that no RCTs were conducted in patients undergoing high-risk surgeries, and that this group is the most likely to benefit from preoperative transfusion. Studies varied regarding inclusion of adults and/or children and the SCD genotype of patients

Six studies reported the effect of preoperative transfusion on the development of postoperative ACS,[138-141,143,144] for which outcomes were variable in degree and effect. One RCT showed that preoperative transfusion reduced the odds of developing postoperative ACS (OR, 0.08; 95% CI, 0.01-0.68), with an anticipated absolute effect of 244 fewer ACS cases per 1000 (95% CI, 70-269 fewer).[138] In contrast, 4 observational studies did not find a significant decrease or a significant increase in ACS in patients receiving preoperative transfusion compared with patients with no transfusion (OR, 1.34; 95% CI, 0.40-4.53).[140,141,143,144] One RCT showed no significant difference in ACS with aggressive preoperative transfusion to decrease the HbS level to less than 30% compared with a conservative preoperative transfusion policy designed to increase the hemoglobin level to 10 g/dL (OR, 0.99; CI, 0.58-1.69).[139]

For postoperative pain crisis prevention, 2 RCTs did not find a significant decrease or increase in postoperative pain crisis with preoperative transfusion compared with no preoperative transfusion (OR, 0.90; 95% CI, 0.19-4.34).[137,138] The meta-analysis of 3 observational studies also did not find a significant difference in postoperative pain crisis between the 2 groups (OR, 1.31; 95% CI, 0.22-7.96).[140,142,143] One RCT reported no significant difference in postoperative pain crisis with aggressive preoperative transfusion compared with the conservative preoperative transfusion policy (OR, 0.55; 95% CI, 0.27-1.41).[139] Three noncomparative studies including 107 patients reported 1 case of mortality each.[147-149] One RCT reported no significant difference in mortality between patients with aggressive preoperative transfusion and those with conservative preoperative transfusion (OR, 5.00; 95% CI, 0.24-104.59).[139]

One RCT[138] and 1 observational study[142] showed no significant difference in alloimmunization rate between preoperative transfusion and no preoperative transfusion (OR, 1.81; 95% CI, 0.29-11.35). One RCT reported an increase in alloimmunization in patients with aggressive preoperative transfusion compared with a conservative preoperative transfusion policy (OR, 2.33; 95% CI, 1.22-4.49).[139] No significant difference in risk for fever, infection, or length of stay between preoperative transfusion and no preoperative transfusion was found.[137,138,141-143,145]

Benefits, harms, and burden. There was an absence of high-quality evidence for the benefits of preoperative transfusion over no preoperative transfusion. There was low-quality evidence from 1 RCT that preoperative transfusion reduced the risk for postoperative transfusion ACS. The guideline panel judged that the prevention of postoperative ACS had a large desirable effect, in view of the high mortality and morbidity associated with ACS. Therefore, despite the very low certainty of evidence, the panel concluded that the balance of effects favored intervention with preoperative transfusion. The sole RCT included patients with HbSS/HbSB^{0}thal undergoing low- to moderate-risk surgery only, and therefore, the panel also concluded that it is difficult to generalize the outcomes from this trial to other genotypes and surgery types, and that an individualized approach to decision-making may be needed.

The potential harms associated with transfusion were considered by the panel to be small. Alloimmunization was the most commonly reported adverse event, but no significant differences in this outcome were seen in the 1 RCT and 1 observational study in which it was reported.[138,142] However, 1 RCT reported an increase in alloimmunization in patients with aggressive preoperative transfusion compared with a conservative preoperative transfusion policy.[139] Using indirect evidence about the risk for alloimmunization and expert opinion, the panel noted that there are subgroups of patients for whom the risk for adverse events from transfusion is increased. These are patients who have multiple red cell alloantibodies or a history of DHTR or hyperhemolysis. For these patients, the risks of preoperative transfusion may outweigh the benefits, and this should be considered when making the decision to offer a preoperative transfusion.

Rationale and key driver for recommendation. The guideline panel concluded that the balance of benefits vs harms favors the intervention of preoperative transfusion in patients with SCD undergoing surgery (supplemental File 5). The benefit of preoperative transfusion was seen in some studies, but not in others. It is unclear whether this variation in outcomes was a result of the low quality of the studies, which were mostly observational, or a result of differing inclusion criteria used in the studies.

Other EtD criteria and considerations. There were little or no data concerning patients with non-HbSS genotypes or with high baseline hemoglobin levels. Some subgroups of patients are likely to benefit more from the intervention than other subgroups of patients, and the decision should be individualized on the basis of the SCD genotype, risk level of surgery, baseline total hemoglobin, history of alloimmunization and/or DHTRs, and disease phenotype.

Technical remarks. For patients for whom preoperative transfusion is considered to be of benefit:

- Simple transfusion is suggested for patients with hemoglobin levels of less than 9 g/dL, and posttransfusion hemoglobin levels should not exceed 11 g/dL;

- exchange transfusion should be considered for patients with hemoglobin levels of greater than 9 to 10 g/dL, aiming for posttransfusion hemoglobin levels of 10 to 11 g/dL; and
- exchange transfusion should be considered for patients undergoing very high risk surgery (neurosurgery or cardiac surgery).

Postoperative transfusion would be appropriate for patients who need emergency surgery and for whom delaying surgery to transfuse preoperatively is unacceptable. It is not possible, from the available evidence, to conclude the optimal preoperative target hemoglobin level or HbS%. Using evidence from the RCT that compared conservative and aggressive preoperative transfusion policies, the panel acknowledges that in patients undergoing low- to moderate-risk surgery, with a pretransfusion hemoglobin level of less than 9 g/dL, the preoperative hemoglobin level is probably more important than the preoperative HbS%, and suggests that clinicians aim for a preoperative hemoglobin level of 9 to 11 g/dL. A low preoperative HbS% (<30% or <50%) is most likely to benefit patients with a very severe phenotype; for example, those with a history of stroke, recurrent ACS, or prior severe postoperative complications.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty of evidence for the use of preoperative transfusion in patients with SCD undergoing low- to moderate-risk surgery under general anesthesia. On the basis of the body of available evidence, preoperative transfusion is more likely to reduce the risk of developing postoperative ACS and acute pain episodes in patients with the SS/SB^0 genotype, a total hemoglobin level of less than 9 g/dL, or a severe phenotype and/or who are undergoing high-risk surgery. The panel identified the following as priority research questions: (1) determining whether preoperative transfusion benefits patients with non-HbSS/SB^0 genotypes undergoing low-, moderate-, and high-risk surgery; (2) determining whether the benefits of perioperative cell salvage in patients with SCD outweigh its risks; (3) determining the optimal preoperative HbS% in patients undergoing high-risk surgery (cardiac surgery or neurosurgery); (4) identifying other modalities to optimize preoperative hemoglobin in patients with SCD (ie, erythroid-stimulating agents or hydroxyurea); and (5) determining whether HbF% affects postoperative outcome for similar levels of preoperative total hemoglobin.

Screening for transfusional iron overload

Should iron overload screening by MRI for cardiac iron content vs serial monitoring of ferritin levels alone be used for patients with SCD receiving chronic transfusion therapy?

Recommendation 10a

The ASH guideline panel *suggests* iron overload screening by MRI (R2, T2*, or R2*) for liver iron content every 1 to 2 years compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- Validated R2, T2*, or R2* methods should be used; if they are not available, the patient should be referred to a specialized center.
- The same method (R2, T2*, or R2*) should be used over time.
- If patients are receiving iron chelation, MRI for liver iron content is helpful for titrating iron chelation, regardless of the ferritin level.
- If the ferritin level is less than 1000 ng/mL and the patient is receiving chronic transfusion by RCE with a neutral or negative iron balance, then MRI for liver iron content is likely not needed.

Recommendation 10b

The ASH guideline panel *suggests against* adding routine iron overload screening by T2* MRI for cardiac iron content compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

- The panel suggests that cardiac T2*MRI screening be performed for the subgroup of patients with SCD with a high iron burden (liver iron content >15 mg/g [dw]) for 2 years or more, evidence of end organ damage resulting from transfusional iron overload, or evidence of cardiac dysfunction.
- If cardiac T2* screening is performed, validated methods should be used, and the same method should be used over time; if these methods are not available, the patient should be referred to a specialized center.

Specific background. Regular red cell transfusions lead to iron accumulation in the liver, heart, and endocrine organs. Complications of iron overload are best described for thalassemia, but differences in iron-related morbidity between SCD and thalassemia exist. Among patients with similar liver iron concentrations, iron-related cardiomyopathy and endocrinopathies are less common in SCD than thalassemia.[151] A number of methods are available to assess the magnitude of iron overload from regular red cell transfusions, and each has its own strengths and limitations. The serum ferritin level test is an inexpensive blood test that broadly correlates with total body iron burden[152] and that, because it can be measured frequently, is useful to monitor trends in iron burden over time. A major limitation in SCD is that inflammation can raise ferritin levels irrespective of iron burden. The liver is the major site of iron accumulation from transfusions, and the liver iron concentration is a good indicator of total iron burden.[153,154] Although liver biopsy was used in the past, noninvasive MRI techniques are now almost exclusively used for this assessment. Both R2 and R2* MRI methods correlate well with iron levels determined by liver biopsy.[155,156] Limitations of MRI include the need for specialized programming and expertise in these MRI techniques, as well as the high cost, which makes frequent monitoring prohibitive. Both ferritin and liver iron concentration do not always predict cardiac iron loading. Heart iron can be estimated using T2* MRI, with values below 20 ms being abnormal. Cardiac T2* measurements can be used to predict the risk of developing iron-related cardiac complications.[157] Cardiac iron loading occurs less commonly in patients with SCD receiving regular transfusions than in transfusion-dependent thalassemia, which brings into question the utility of regular cardiac iron monitoring in SCD. The optimal mode and

frequency of liver and cardiac iron overload screening for chronically transfused patients with SCD are not well established.

Summary of the evidence. The systematic review identified 4 noncomparative observational studies (total, 267 patients). Studies were examined for the following outcomes: iron-induced liver disease/liver failure, cardiac disease, and endocrinopathies (growth failure, delayed puberty, hypothyroidism, and diabetes), as well as mortality. There were no studies that compared screening for iron-induced liver disease using MRI vs serial monitoring of ferritin levels. One retrospective study of 22 patients with SCD showed that the quantification of hepatic iron on 3T MRI correlated significantly with ferritin level and liver biopsy (only 2 subjects had MRI and biopsy within 6 months).[154] In addition, 2 of 4 patients with abnormal ALT values had high T2* liver iron concentration above 10 mg/g (dw), suggesting that MRI may be useful in predicting iron-induced liver disease. There were also no studies that compared screening for iron-induced cardiac disease using MRI vs serial monitoring of ferritin level. Three observational studies showed an extremely low prevalence of cardiac T2* abnormalities in transfused patients with SCD, and evidence of cardiac iron loading developed only with prolonged elevated liver iron concentration.[158-160] One study of 9 chronically transfused pediatric patients with SCD showed no abnormal cardiac T2*[158]; 4 had ventricular dilatation. A second study also showed that among 41 chronically transfused patients with SCD with a mean age of 22.9 years, none developed a cardiac T2* of less than 20 ms during 2 years of follow-up.[159] In the third study, 6 of 201 patients developed cardiac iron overload; these 6 patients had poor chelation compliance, serum ferritin levels of more than 4600 ng/mL, and elevated liver iron concentrations of more than 22 mg/g (dw).[160] No studies reported iron-induced endocrinopathies or mortality with regard to MRI monitoring of iron overload.

Given the paucity of direct evidence, the panel considered indirect evidence to support the recommendations. The limitation of serum ferritin to estimate iron burden in SCD was evidenced in a number of studies. One observational study showed wide variability in the rise of ferritin in 61 children with SCD who initiated regular transfusions for primary stroke prevention. Multiple studies showed that ferritin levels do not correlate precisely with liver iron concentration in SCD,[91,161-163] and trends in ferritin levels show similar limitations.[164-166] Low ferritin levels (<1500 ng/mL) generally correlate with well controlled liver iron concentration: in 1 study, 90% of patients with serum ferritin below 1500 ng/mL had liver iron concentration below 7 mg/g (dw), whereas in another, serum ferritin values of 750 to 1500 ng/mL corresponded to liver iron concentration of 2.5 to 10 mg/g dw in 75% of patients.[164,166] Conversely, ferritin levels above 2500 to 3000 ng/mL usually are associated with high liver iron concentrations above 10 to 15 mg/g dw, although with exceptions.[91,161] Higher liver iron concentration is associated with increased liver fibrosis in SCD.[162,166]

Benefits, harms, and burden. The panel judged the desirable effects of liver MRI to be moderate, and those of cardiac MRI to be small. Given the limitations of serum ferritin level in predicting liver iron concentration, liver MRI by the R2 or R2* method allows an estimation of liver iron concentration that may be used to adjust chelation regimens. Because liver fibrosis and elevated ALT are more common with high liver iron content, assessment with appropriate treatment may help prevent liver injury. In addition, as cardiac iron loading generally is evidenced in SCD only with prolonged elevated liver iron content, liver R2 or R2* MRI monitoring could identify patients at risk for that complication. However, the certainty of the evidence is very low.

The panel judged the undesirable effects of liver MRI to be trivial. Little information is provided in the observational studies about potential harm of MRI, although the risks for MRI are small. The panel acknowledges the high cost of the test. The liver MRI was judged to be probably acceptable with variable feasibility.

Rationale and key driver for recommendation. Given the significant limitations of serum ferritin levels in SCD, the guideline panel determined that regular assessment of liver iron concentration by R2 or R2* MRI is indicated in chronically transfused patients (supplemental File 5). Liver MRI assessment may not be needed in patients with very low serum ferritin levels, particularly if managed with regular exchange transfusions, given that low ferritin levels usually predict low liver iron concentration in patients with SCD. Given that cardiac iron loading is very uncommon in SCD, the guideline panel determined that routine assessment of cardiac T2* is not warranted for all chronically transfused patients with SCD, but should be considered for individuals with a high iron burden (liver iron content >15 mg/g [dw]) for 2 years or more, history of exceptionally elevated liver iron, evidence of end organ damage resulting from transfusional iron overload, or evidence of cardiac dysfunction (supplemental File 5). If cardiac T2* is warranted, some cardiac MR facilities can offer both cardiac and liver iron measurements in a single imaging procedure.

Technical remarks. The use of MRI for iron estimation requires special acquisition sequences and postacquisition analysis; patients should be referred to specialized centers with appropriate expertise in these methods. Both R2 and R2* MRI methods have shown good correlation with liver iron concentration obtained by liver biopsy; R2 and R2* results correlate well ($r^2 = 0.93$) with each other.[167] Because systematic bias exists between R2 and R2* methods, particularly at very low and high liver iron concentrations,[167] the same MRI method should be used over time if possible.

Conclusions and research needs for this recommendation. The guideline panel concluded that MRI screening for liver iron concentration should be performed every 1 to 2 years in patients with SCD receiving chronic transfusion therapy, but that cardiac T2* monitoring should not be routinely performed unless there is a history of poorly controlled iron burden. The panel identified the following research priorities: (1) prospective studies to understand the clinical significance of varying degrees of iron overload in patients with SCD, including correlation with organ dysfunction, SCD-related complications, and mortality; (2) a prospective, randomized trial of deferasirox compared with deferiprone for the treatment of transfusion iron overload in SCD; and (3) prospective studies of the prevalence of abnormal cardiac T2* MRI, including investigation of potential risk factors such as genetic predisposition and chelator type.

What are others saying, and what is new in these ASH guidelines?

Transfusion support for patients with SCD is addressed within existing guidelines for SCD and overlaps several of the topics prioritized for these ASH guidelines. The most relevant guidelines are the 2014 National Heart, Lung, and Blood Institute Expert Panel Report of the Evidence-Based Management of Sickle Cell Disease,[12] the 2018 Standard for Clinical Care of Adults with Sickle Cell Disease in the United Kingdom,[168]

the 2018 International Collaboration for Transfusion Medicine Guidelines on Red Blood Cell Specifications for Patients with Hemoglobinopathies,[13] and the 2019 Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society of Apheresis.[84]

Red cell antigen profiling and matching are addressed in several of the existing guidelines. The ASH transfusion panel along with the Mayo Clinic systematic review team extracted primary alloimmunization data from the literature and calculated alloimmunization rate per 100 units transfused, which increased the certainty of evidence to moderate and supported a strong recommendation for prophylactic Rh (C, E or C/c, E/e)- and K-matched red cells for patients with SCD. This differs from the 2014 National Heart, Lung, and Blood Institute and the 2018 International Collaboration for Transfusion Medicine Guidelines, which graded evidence regarding antigen matching as low quality and resulted in moderate and weak recommendations, respectively.

The recommendations made in the current guidelines for preoperative transfusion, transfusion of pregnant women, and iron overload screening align with 2014 National Heart, Lung, and Blood Institute and 2019 UK standards. Recommendations on the mode of transfusion for chronically transfused patients with SCD (simple vs RCE), the use of isovolemic hemodilution with RCE, and the use of immunosuppressive therapy for prevention or treatment of acute and delayed HTRs are uniquely included in the ASH Transfusion Support Guidelines, whereas other guidelines have not addressed these clinical questions.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty of the evidence identified for many of the questions. The included studies did not measure the potential burden of blood transfusion, which include emotional distress, time required to undergo transfusion, associated loss of income, and patients' concerns about transfusion. The guideline panel acknowledged that several recommendations have "moderate resource implications" associated with them because of the cost of transfusion and the requirement for exchange transfusion in certain patient scenarios.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[169]

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Authorship

Contributions: S.T.C. wrote and revised the manuscript based on authors' suggestions; guideline panel members R.M.F., J.J.F., J.E.H., J.H., M.K., J.L.K., F.P., P.A.S., S.R.S., S.L.T., C.M.W., T.E.W., and E.A.A. critically reviewed the manuscript and provided suggestions for improvement; M.A., a member of the knowledge synthesis team, contributed evidence summaries to the guidelines; S.T.C. and E.A.A. were the cochairs of the panel and led the panel meeting; panel members each assisted in writing the first draft of 1 recommendation for the manuscript; and all authors approved of the content.

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