CLINICAL GUIDELINES

blood advances

American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation

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Background: Sickle cell disease (SCD) is a life-limiting inherited hemoglobinopathy that results in significant complications and affects quality of life. Hematopoietic stem cell transplantation (HSCT) is currently the only curative intervention for SCD; however, guidelines are needed to inform how to apply HSCT in clinical practice.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and health professionals in their decisions about HSCT for SCD.

Methods: The multidisciplinary guideline panel formed by ASH included 2 patient representatives and was balanced to minimize potential bias from conflicts of interest. The Mayo Evidence-Based Practice Research Program supported the guideline development process, including performing systematic evidence reviews (through 2019). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 8 recommendations to help patients and providers assess how individuals with SCD should consider the timing and type of HSCT.

Conclusions: The evidence review yielded no randomized controlled clinical trials for HSCT in SCD; therefore, all recommendations are based on very low certainty in the evidence. Key recommendations include considering HSCT for those with neurologic injury or recurrent acute chest syndrome at an early age and to improve nonmyeloablative regimens. Future research should include the development of a robust SCD registry to serve as a comparator for HSCT studies.

Summary of recommendations

Sickle cell disease (SCD) is the most common inherited clinically significant hemoglobinopathy in the United States. Individuals with SCD are affected by multiple disease-related complications that result in significant morbidities and early mortality. Hematopoietic stem cell transplantation (HSCT) is currently the only established curative intervention for SCD that can restore normal hematopoiesis. The American Society of Hematology (ASH) guideline panel addressed questions related to the use of HSCT for patients with SCD with neurologic injury, frequent pain, or acute chest syndrome (ACS). The panel also addressed questions related to the type of transplantation and donor used and age of the patient.

Submitted 28 January 2021; accepted 23 June 2021; final version published online 28 September 2021. DOI 10.1182/bloodadvances.2021004394.

The full-text version of this article contains a data supplement.

This guideline is based on updated and original systematic reviews of evidence conducted under the direction of the Mayo Evidence-Based Practice Research Program. The panel followed best practices 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, and 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 in the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation

- For patients: A 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.
- For clinicians: Different choices will be appropriate for individual patients, and clinicians 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 research gaps.

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.[12] Good practice statements in this guideline are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Values and preferences

The recommendations for HSCT in patients with SCD are presented in terms of the primary SCD-related complications of concern, the age of the patient, and the type of transplantation under discussion. The importance of the patient's and family's preferences remained central to the discussion and associated recommendations. These recommendations, however, are generally based on low certainty in the evidence. This dearth of data underscores the importance placed on individualized patient care that involves shared decision making between the provider and the patient and family. Furthermore, the balance of benefits and harms differs in children and adults when considering transplantation, both because of the increased risk of HSCT in adults with SCD and potential gain in those with accumulated SCD-related comorbidities. Therefore, it is particularly important to adjust for patient and family preferences and to consider individual patient/family values and risk threshold in the context of past experiences with SCD.

Other evidence to inform decision criteria and considerations

The panel recognizes that there may be significant uncertainty or variability in how much people value the main outcomes of HSCT as a result of insufficient knowledge regarding the risks and benefits of myeloablative vs nonmyeloablative or reduced-intensity conditioning (RIC) and alternative donor HSCT. In addition, there are no clear classification systems to determine if a patient with SCD has severe disease or if the patient will experience specific SCD complications in their life course. Therefore, it can be difficult to accurately balance a risk/benefit ratio of HSCT that takes into account an individual patient's lifetime experience. However, there is an assumption that living without SCD is preferred over having unpredictable and debilitating complications that increase with age. In contrast, HSCT-specific harms have been documented in several studies. These include graft-versus-host disease (GVHD), infections, graft failure, infertility, vital organ injury, and death. These transplantation-related risks are detailed in the methodologic considerations below (Table 3). Because these potential harms are not insignificant, they must be considered along with the potential benefits that include a cure for SCD.

The panel was not able to assess how substantial the desirable anticipated effects may be, because the extent and duration of benefit of HSCT are not known as a result of incomplete long-term follow-up data post-HSCT. Furthermore, the cost of transplantation compared with that of standard of care is also not established. Although the costs of HSCT are significant in the short term, they may be offset by the reduced hospitalizations, decreased transfusions, and termination of costly SCD-specific medications that would no longer be required when HSCT is successful. Additionally, the potential gains from improved ability of affected individuals to attend school and work could also help counterbalance the long-term costs of HSCT. The feasibility of HSCT is also complicated because of concerns with lack of trust on behalf of the patients, insufficient donor availability, preexisting comorbidities, and poor access to care, including lack of access to a transplantation facility. In more recent years, feasibility of HSCT has substantially increased because of improvements in the process of donor-recipient HLA match requirements and less toxic

conditioning regimens that are more suitable for patients with preexisting comorbidities.

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, the cost effectiveness of most interventions could not be assessed.

Recommendations

Recommendation 1. The ASH guideline panel *suggests* HLA-matched related HSCT rather than standard of care (hydroxyurea (HU)/transfusion) in patients with SCD who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound (TCD) (conditional recommendation. very low certainty in the evidence ⊕◯◯◯).

Remarks:

- Consideration for transplantation should occur in all patients with neurologic injury who have a matched related sibling donor.
- When considering transplantation for neurologic injury, children younger than age 16 years who receive matched sibling donor (MSD) HSCT have better outcomes than those older than age 16 years.

Recommendation 2. For patients with frequent pain, the ASH guideline panel *suggests* using related matched allogeneic transplantation rather than standard of care (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Consideration for transplantation should be given to patients who do not respond or have an inadequate response to standard of care, such as HU, new targeted therapies, or chronic transfusion therapies.

Recommendation 3. For patients with recurrent episodes of ACS, the ASH guideline panel *suggests* using matched related allogeneic transplantation over standard of care (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Consideration for transplantation should be given to patients who continue to have recurrent ACS despite optimal standard of care (eg, HU, L-glutamine, crizanlizumab, and chronic transfusion therapy).

Recommendation 4. For patients with SCD with an indication for HSCT who lack an MSD, the ASH guideline panel *suggests* using transplants from alternative donors in the context of a clinical trial (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Alternative donor transplantation has the potential to improve or resolve disease manifestations in patients with severe SCD. The risks related to transplantation complications should be balanced with benefits derived from successful transplantation.

Recommendation 5. For allogeneic HSCT, the ASH guideline panel *suggests* using either total-body irradiation (TBI) ≤400 cGy or chemotherapy-based conditioning regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 6a. For children with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* using myeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 6b. For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* nonmyeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 7. In patients with an indication eligible for HSCT, the ASH guideline panel *suggests* using allogeneic transplantation at an earlier age rather than an older age (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Recommendations could not be made if an MSD was not available because of the paucity of available data.
- The impact of age on HSCT outcome may also be affected by the conditioning regimen used.

Recommendation 8. The ASH guideline panel *suggests* the use of HLA-identical sibling cord blood when available (and associated with an adequate cord blood cell dose and good viability) over bone marrow (BM) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Introduction

Aims of this guideline and specific objectives

The purpose of this guideline is to provide evidence-based recommendations for HSCT for SCD. The primary goals of this guideline are to review and critically appraise the existing literature and provide recommendations for patients and health care professionals to support their decision making. Through improved provider and patient education using the available evidence and evidence-based recommendations, this guideline aims to provide clinical decision support for shared decision making that will help identify which individuals with SCD should be considered for HSCT.

The target audience for this guideline includes patients, hematologists/HSCT providers, general practitioners, internists, other clinicians, and decision makers. Policy makers interested in these guidelines may include those involved in developing local, national, or international plans with the goal of improving the health of 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

HSCT is a potential 1-time curative therapy for SCD. Although considered acceptable therapy for many malignant and nonmalignant hematologic disorders, the use of HSCT in SCD continues to evolve, with new conditioning regimens, alternative donors and methods of cell harvesting, and strategies for GVHD prevention. Furthermore, as success rates after HSCT are improving, so too are survival rates in children and adults with SCD receiving disease-modifying medication and supportive therapy. Therefore, there are many questions regarding optimal use of HSCT in SCD. The risk of harms associated with HSCT must be considered when asking questions related to the use of transplantation in SCD, especially when there are approved targeted therapies (eg, HU, L-glutamine, voxelotor, and crizanlizumab) and new potentially curative therapies under development (eg, gene therapy). As a result, the panel focused predominantly on (a) which individuals with SCD should be considered for HSCT based on specific SCD complications and age, (b) what type of transplantation should be offered in terms of conditioning (ie, myeloablative, nonmyeloablative, or reduced intensity), and (c) what type of donor should be used (ie, matched related donor, haploidentical related donor, or matched unrelated donor [MUD]), including stem cell source (ie, marrow, peripheral blood, or umbilical cord blood [UCB]). Final questions evaluated by the panel had to have the potential for answers within the available published data. Therefore, questions regarding the safety and efficacy of gene-corrected autologous HSCT, which are only now emerging, were not considered in these guidelines.

The first allogeneic transplantation for SCD was reported in 1984 in a pediatric patient with SCD and acute myelogenous leukemia, who was ultimately cured of both diseases.[13] Since then, >1000 individuals with SCD have undergone HSCT, predominantly using HLA-identical sibling donors, with >90% of all such patients cured of SCD reported in the short-term follow-up.[14] HSCT is an established therapeutic option for patients with SCD with a clinical indication and an HLA-identical sibling donor. Unfortunately, <20% of patients with SCD in the United States have an MSD, and a similar percentage have an MUD in the registry,[15,16] meaning that most patients who might wish to pursue HSCT will lack a well-matched donor. Alternative donors, including unrelated, unrelated UCB, and haploidentical related donors have improved access to HSCT. However, improved options must balance the potentially increased risks associated with these donor options.

This work represents the first attempt to develop guidelines for allogeneic HSCT in SCD based upon the available evidence. As the options and outcomes improve for allogeneic HSCT in SCD, this guideline may provide the basis for future periodic refinement.

The recommendations are presented according to the transplantation indication based on SCD complication and then based on patient age and type of transplantation under consideration. Throughout the recommendations, the panel notes the importance of the preferences of the patients, their families, and their support structures in these discussions.

There are no randomized clinical trials comparing HSCT and conservative treatment of SCD; therefore, all the recommendations in this guideline are supported by very low certainty in the evidence. Furthermore, the balance of benefits and harms of transplantation may be different in children and adults; therefore, decisions about when to use transplantation must be individualized according to patient and family values and preferences, especially values about the risk of harms. How benefits and harms are balanced may also depend on setting and access to standard treatments that may not be universally available (eg, in places where survival for children with SCD is not close to 100%, such as in middle-income nations,[17-19] transplantation could be viewed more favorably as a treatment option). This guideline takes the perspective of high-resourced settings.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[5-11] 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 (GIN)–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.[1-4]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 4 other guideline panels (addressing other aspects of SCD) by ASH and the Mayo Evidence-Based Practice Research Center (funded by ASH under a paid agreement). Project oversight was provided by a coordination panel, which reported to the ASH Guideline Oversight Subcommittee. ASH vetted and appointed individuals to the guideline panel. The Mayo Center vetted and retained researchers to conduct systematic reviews of evidence and coordinated the guideline development process, including the use of the GRADE approach.[8] The membership of the panels and the Mayo Center team is described in Supplement 1.

The panel included hematologists, HSCT specialists, other physicians, and patient stakeholders, including a recipient of a failed HSCT and the mother of a patient who underwent a successful HSCT, who all had clinical and research expertise on the guideline topic; 1 co-chair was an HSCT expert, and the other co-chair was a guideline development methodology expert.

In addition to synthesizing evidence systematically, the Mayo Center supported the guideline development process, including determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The panel's work was performed using Web-based tools (www.gradepro.org) and online and face-to-face 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 honorariums of $100 per day for in-person meetings and $25 per conference call. The panelists received no other payments. 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 according to recommendations of the Institute of Medicine[102] and the GIN.[1] 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, including individuals not expert or specialized in providing transplantation. On appointment, no panelists were considered to have direct financial conflicts with for-profit companies that could be directly affected by the guideline. For example, companies that market chemotherapy products used for conditioning prior to transplantation could be affected by recommendations about the use of those products. None of the Mayo-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts. A few panelists reported financial relationships with for-profit companies that could be considered indirectly affected by the guidelines (eg, companies investigating curative nontransplantation therapies such as gene therapies).

There was 1 deviation from usual ASH policy. When the panel was formed, it was expected that recommendations about stem cell source would be out of scope. Therefore, direct financial relationships with companies that store and sell UCB and stem cells were not initially considered a conflict of interest. However, recommendation 8 does address stem cell source, (ie, favors cryopreserved cord blood over BM). Because ASH staff did not note this, 2 panelists participated in forming the recommendation despite their direct financial relationships with cord blood banks. Under usual ASH policy, they should have been recused from making judgments on or voting about individual domains (eg, magnitude of desirable consequences) or the direction or strength of the recommendation. After the recommendation was formed, and during the approval of this guideline, members of the Guideline Oversight Subcommittee agreed to allow this as a deviation from usual policy.

Supplement 2 provides the complete disclosure of interests forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years prior to appointment; in part B, indirect financial interests; and in part C, 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.

Supplement 3 provides the complete disclosure of interests 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 described in Table 1.

The panel selected outcomes of interest for each question a priori (Table 2), following the approach described in detail elsewhere.[20] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach.[20]

While acknowledging considerable variation in the impact on patient outcomes, the panel considered the following outcomes as critical for clinical decision making across all questions. All questions identified the same initial primary outcomes of interest, including disease-free survival, overall survival (OS), acute and chronic GVHD, and graft failure/graft rejection. Additional primary outcomes of interest were based on the question of interest for each question and were asked a priori.

Evidence review and development of recommendations

For each guideline question, the Mayo Center prepared a GRADE Evidence-to-Decision (EtD) framework using the GRADEpro Guideline Development Tool (www.gradepro.org).[6-8] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed 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 that recent studies were not missed in addition to searches presented in supplement 4, panel members were asked to suggest any studies that may have been missed that fulfilled the inclusion criteria for the individual questions.

Table 1. Questions prioritized by the guideline panel

Prioritized questions
Q1: Should individuals with SCD and neurologic injury, including overt stroke, SCI, or abnormal TCD, undergo MSD transplantation?
Q2: Should individuals with frequent pain requiring interventions by a health care provider undergo MSD vs standard of care?
Q3: Should individuals with recurrent episodes of ACS undergo matched related allogeneic transplantation vs standard of care?
Q4: Should individuals with SCD with an indication for HSCT (as above) who do not have an MSD undergo nonmyeloablative transplantation from alternative donor vs standard supportive care?
Q5: Should individuals with SCD undergoing allogeneic transplantation receive a TBI-based regimen (low-dose TBI ≤400 cGy) or chemotherapy-based regimen?
Q6: Should individuals with SCD and an indication for HSCT (as above) and an MSD receive myeloablative conditioning or RIC or nonmyeloablative conditioning?
Q7: Should age be a determining factor for HSCT with an MSD for individuals with SCD with the above indication?
Q8: In pediatric patients with SCD, an indication for BM transplantation, and available cryopreserved matched sibling UCB, should myeloablative BM transplantation be used vs myeloablative UCB transplantation?

SCI, silent cerebral infarct.

Table 2. Outcomes prioritized by the guideline panel

Question	Secondary outcome of interest
Q1: Should individuals with SCD and neurologic injury (overt stroke, SCI, or abnormal TCD) undergo MSD transplantation?	1. Improvement/normalization of TCD velocity 2. Primary ischemic stroke 3. Secondary ischemic stroke 4. New or progressive SCI 5. New or progressive CNS vasculopathy 6. HRQOL 7. Engraftment kinetics
Q2: Should individuals with frequent pain requiring interventions by a health care provider undergo MSD HSCT vs standard of care?	1. Change in frequency of acute pain episodes requiring acute care 2. Change in hospitalization frequency 3. HRQOL 4. Engraftment kinetics
Q3: Should individuals with recurrent episodes of ACS undergo MSD HSCT vs standard of care?	1. Change in frequency of ACS 2. Change in hospitalization frequency 3. Resolution or improvement in chronic lung disease 4. HRQOL 5. Engraftment kinetics
Q4: Should individuals with SCD with an indication for HSCT (as above) who do not have an MSD undergo nonmyeloablative transplantation from alternative donor vs standard supportive care?	Same as Q1-3
Q5: Should individuals with SCD undergoing allogeneic transplantation receive a TBI-based regimen (low-dose TBI ≤400 cGy) or chemotherapy-based regimen?	Same as Q1-3 Additional outcome: potential for fertility post-HSCT
Q6: What is the optimal conditioning regimen for individuals with SCD who have an indication for HSCT and a matched sibling donor (myeloablative transplantation vs reduced intensity or nonmyeloablative transplantation)?	Same as Q 1-3 Additional outcome: Potential for fertility post-HSCT
Q7: Should age be a determining factor for HSCT with MSD for individuals with SCD with the above indication?	Same as above (Q6)
Q8: In pediatric patients with SCD undergoing matched related donor HSCT with available cryopreserved matched sibling cord blood use the cord blood or BM as donor source?	Same as above (Q6)

CNS, central nervous system; HRQOL, health-related quality of life.

Under the direction of the Mayo Center, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for updating or conducting new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of 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 of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized controlled trials (RCTs) 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.[6-8]

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 of bias, precision, consistency, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[9-11] Within this report, these categories are represented by the symbols, as follows:

⊕⊕⊕⊕ High certainty in the evidence about effects
⊕⊕⊕◯ Moderate certainty in the evidence about effects
⊕⊕◯◯ Low certainty in the evidence about effects
⊕◯◯◯ Very low certainty in the evidence about effects

Interested readers may find more explanation about the GRADE approach to assessing and rating certainty in a body of evidence in other publications.[21-27]

During 2 separate 2-day in-person meetings, followed by online communication and conference calls, the panel developed 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 in 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 guideline, including recommendations, was reviewed and approved by all members of the panel. The approach is described in detail in the accompanying article describing the methods of development.[28]

Special methodologic considerations

1. A systematic review of HSCT in SCD was performed to assess the effects of transplantation on outcomes of interest. Because of variation in the components of standard of care, pooling of results across studies of standard of care was not performed. Instead, the panel identified published systematic reviews and key RCTs

that separately evaluated various types of standards of care and compared those with transplantation trials to derive its recommendations.

2. There were insufficient numbers of HSCTs with nonmatched sibling donors (alternative donor transplantation) and high variability in HSCT approaches in reports differing in types of nonmyeloablative conditioning or RIC regimens in the literature to draw valid conclusions. Therefore, the guideline development group collaborated with the Center for Blood and Marrow Transplant Registry (CIBMTR), a working group of >300 transplantation centers that contribute data on consecutive allogeneic and autologous transplantations. The aim was to determine the relative effects of donor type (unrelated donor vs UCB vs haploidentical relative), HSC source (peripheral blood vs BM), and transplantation conditioning intensity on outcomes in patients after HSCT with SCD. The primary outcome of interest was event-free survival (EFS; death from any cause or graft failure with or without recurrent SCD as cause of treatment failure). Other outcomes studied were OS (death from any cause) and acute and chronic GVHD based on standard criteria. The methods and statistical analysis have been previously published.[29] In brief, the analysis compared the characteristics of patients by donor type or categorical variables and used a cumulative incidence estimator to assess the probabilities of graft failure and acute and chronic GVHD compared with other risks. Variables considered included age, sex, performance score, hematopoietic cell transplantation comorbidity index, recipient cytomegalovirus serostatus, donor type, conditioning regimen intensity, graft type, and transplantation period. Age was treated as a binary variable (≤12 vs 13-49 years). Importantly, the age cutoff at <13 years was determined statistically as the optimal cut point in the Cox regression model for overall mortality. Conclusions from this analysis were used in the development of the guideline recommendations.
3. There is a clear difference between the recommendation of transplantation for children living with SCD compared with that for adults. Throughout the guideline process, the panel discussed the differences in the potential benefits and harms between children and adults. These differences are reflected in the final recommendations, where the population is clearly identified in the recommendation (ie, "In children with SCD…" or "In adults with SCD…"). In addition, these differences are reflected in the distinction made regarding the strength of the recommendation and certainty in the evidence. Technical remarks also include information pertinent to specific age groups.
4. The harms of HSCT were evaluated generally with various conditioning, donor types, and stem cell sources (Table 3). These potential harms were considered in every recommendation when balancing benefits and harms.
5. For all recommendations, in addition to health effects, the panel also considered other important elements. These included feasibility, resource requirements, and the impact on health care equity of transplantation in comparison with standard care. The panel also considered how patients and families may value the adverse health effects of the interventions relative to potential gains. These are included for specific questions in the EtD criteria and considerations.

Table 3. Potential harms (complications and adverse effects) of HSCT

Complication	Description
Death	Survival after HLA-identical sibling donor HSCT varies by age. In a large retrospective analysis of HSCT in patients with SCD, mortality occurred in 5%-20% depending on age.[14] The probabilities of OS and EFS are summarized below: For patients <16 y of age: OS, 95% EFS, 93% For patients ≥16 y of age: OS, 81% EFS, 77% In a more recent analysis of the data by CIBMTR, a higher incidence of mortality was observed in patients >13 y of age following myeloablative conditioning and MSD HSCT.[30]
GVHD	The development of GVHD after HSCT was a significant concern voiced by some patient representatives. The thought of dealing with a new chronic disease, like chronic GVHD, might be perceived as worse than SCD for some patients, although it is possible that some may consider this an acceptable risk, depending on severity, if balanced by cure from SCD. The incidence of GVHD after MSD HSCT and myeloablative conditioning is summarized below: For patients ≤16 y of age: acute GVHD (grade 2-4), 12.6% chronic GVHD, 14.6% For those >16 y of age: acute GVHD (grade 2-4), 16% chronic GVHD, 23%
Graft failure	For some individuals considering HSCT, the biggest risk is that the procedure fails, and they have recurrent SCD. Graft failure is most often manifested as autologous recovery and therefore recurrence of the SCD manifestations. Risk of graft failure varies by conditioning intensity, donor type, GVHD prophylaxis (eg, use of T-cell depletion), and HLA match. After MSD HSCT, graft failure occurs in 5%-10% of patients.[14] The risk of graft rejection increases as the conditioning regimen intensity decreases and if an alternative donor (HLA mismatched or unrelated) is used. Although less frequent than GVHD, the risk of graft failure may carry a larger emotional burden than other HSCT complications and should be thoroughly discussed with potential patients and families as well as familial donors if applicable.
Infection	Infection is a common complication of SCT but is usually manageable. In many instances, infection may prolong hospitalization or cause additional hospitalizations in individuals who have undergone SCT. In rare instances, infections might not respond to available treatment and could be fatal. The risk decreases over time after SCT and as immune suppression is stopped. Infection is a common complication of GVHD.
Infertility	Infertility risk after HSCT is an important consideration for all patients and in those with SCD. Infertility occurs frequently after myeloablative conditioning and is nearly universal in postpubertal patients. However, with the advent of less intense conditioning, the risk of infertility is likely lower. The option of gamete retrieval and cryopreservation is an increasingly considered option, although it is expensive and not universally available. This is an important consideration in patient decision making
Malignancy	The incidence of a therapy-related malignancy, particularly after myeloablative allogeneic HSCT, seems to be low overall.[29] Risks after less intense conditioning regimens are not known at this time. This risk should be discussed with potential patients and families.

a. Feasibility. With respect to feasibility, the panel noted that across settings, even in a high-resource country such as the United States, HSCT may not be feasible. Within the United States, feasibility varies by location, patient socioeconomic status, or third-party payer. Feasibility is more substantially problematic in resource-poor settings where the lack of access to supportive care sufficient for transplantation precludes implementation. However, issues such as proximity to a transplantation center, missed employment, and payment are significant and may limit universal feasibility.[31]
b. Required resources. HSCT is a costly intervention. If HSCT is pursued during childhood, and it is assumed that the duration for which the patient will be free of the disease is lifelong, there will be large health care savings over the lifespan of the cured individual. When undergoing transplantation as an adult, there will be lower health care savings. Resources are needed for individuals undergoing transplantation and their support systems regardless of age that are not always or not often covered by insurance and may limit feasibility for individuals.
c. Equity. Access to HSCT is not universal and often depends upon socioeconomic status and adequate health care coverage. In addition, the transplantation center may be far away from the patient's home, necessitating additional financial burdens in addition to separation from family and work.
d. Justification. The risk of adverse events (harms discussed above) are balanced against benefits of not having SCD and likelihood of increased survival.

How to use this guideline

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. This guideline is 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, or availability of treatments. This guideline 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 this guideline cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in this guideline.

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 this guideline. Implementation of the guideline will be facilitated by forthcoming decision aids.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online from 11 April 2019 until 13 May 2019 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Nine individuals and 2 organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On 1 January 2021, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality agreed that the defined guideline development process was followed, and on 15 January 2021, the officers of the ASH Executive Committee approved submission of the guideline for publication under the imprimatur of ASH. The guideline was then subjected to peer review by *Blood Advances*.

Recommendations

Recommendation 1

Should individuals with SCD and neurologic injury (overt stroke or abnormal TCD) undergo MSD transplantation?

Recommendation 1

The ASH guideline panel suggests HLA-matched related HSCT rather than standard of care (HU/transfusion) in patients with SCD who have experienced an overt stroke or have an abnormal TCD (conditional recommendation, very low certainty in the evidence ⊕◯◯◯).

Remarks:

- Consideration for transplantation should occur in all patients with neurologic injury who have a matched related sibling donor.
- When considering transplantation for neurologic injury, children younger than age 16 years who undergo MSD HSCT have better outcomes than those older than age 16 years.

Specific background. Neurologic injury caused by overt stroke and SCI is a major complication of SCD. Early large retrospective observational studies demonstrated that for people with sickle cell anemia (HbSS or HbSB0), up to 24% could be affected by stroke.[32] These studies also showed that chronic red cell transfusion (CRCT) and other supportive care therapy were useful in stroke prevention but not curative.[33] Furthermore, in the absence of chronic red blood cell (RBC) transfusions, ~67% of at-risk children will have a second overt stroke.[34] However, long-term CRCT is associated with risks such as alloimmunization and transfusional iron overload. Therefore, efforts to prevent primary or secondary stroke have focused on curative options such as HSCT.

Summary of the evidence. The panel reviewed outcomes related to neurologic injury: abnormal cerebral blood flow as measured by TCD, primary ischemic stroke, secondary ischemic stroke, and new or progressive SCI. There were no RCTs comparing standard treatment of primary or secondary stroke prevention and HSCT. Studies reviewed included those SCD studies aimed at stroke prevention and those HSCT studies that included neurologic outcomes in their publications. A total of 31 studies were available for evaluation.

In summary, trials aimed at stroke prevention demonstrated that CRCT can reduce the risk of first ischemic stroke in children with an abnormal TCD. Children without significant CNS vasculopathy can be safely transitioned from CRCT to HU.[35] However, CRCT remains the only option for disease stabilization in children with a previous

ischemic stroke but is not always effective. Four trials[15,36-38] conducted from 1991 to 2011 included children who underwent HSCT for prevention of primary or secondary stroke as their indication for HSCT. The accumulated findings suggested stabilization of CNS pathology on magnetic resonance imaging or a decrease in stroke rate after HSCT compared with standard of care. Only 1 recent trial, DREPAGREFFE, compared outcomes of HSCT with those of standard of care in children with SCD who had an abnormal TCD.[39] Overall, the HSCT group had more children who developed a normal TCD compared with standard of care. In this study, new SCI was found in 3 children and cerebral arterial stenosis in 2 children receiving standard care, whereas neither was observed after HSCT. There are no studies that have been intentionally conducted in persons with SCD with SCI alone (who did not have a history of overt stroke or abnormal TCD) to evaluate the impact of HSCT on SCI alone.

Benefits. The panel agreed that HSCT has moderate anticipated benefits for patients who have had a stroke or are at risk of having a stroke, including protection from progressive neurovascular disease without ongoing supportive care. The protective effect seems to be equivalent, if not superior, to that observed with regular RBC transfusions. Overall, the certainty of these estimated effects is very low, because the only comparative trial relied upon a surrogate outcome measurement (cerebral arterial velocity measured by TCD) of stroke prevention.

Harms and burdens. There are several health-related risks associated with HSCT (Table 3). The evaluations of each potential harm depend on the type of transplantation, the type of conditioning regimen/chemotherapy, and the age of the individual. These potential harms and burdens are universally associated with HSCT but may be of greater or lesser risk based on degree of SCD-related complications, age, or type of transplantation. The risk of graft failure/rejection or GVHD is low to moderate in individuals who receive a matched related donor transplant. Infection risk is higher with myeloablative therapy.[40] The guideline panel estimated the risk of death in MSD HSCT to be small. The risk of infertility is high after myeloablative HSCT. The risk of malignancy is low after myeloablative HSCT.

Rationale and key drivers for this recommendation. On the basis of very low certainty in the evidence from noncomparative studies, the panel judged that the balance of benefits (cure and increased survival) and harms (infertility, GVHD, and death) probably favors HSCT for individuals with SCD with neurologic complications. However, given the available evidence, the guideline panel considered the risk of adverse effects is probably small for most patients and their providers.

EtD criteria and considerations. The panel noted that the most common reason cited for a referral to HSCT for SCD is overt ischemic stroke. In addition, patients and their families place a high importance on stopping lifelong RBC transfusions. The panel agreed that there is a potential for decreased interruption of work/school/activities if frequent clinic or transfusion visits are not required. The panel also agreed that there may be possibly important uncertainty or variability in how much people value the main outcomes of preventing neurologic complications, including understanding the risk of stroke/recurrent stroke and outcomes related to stroke, existing treatment options, or the possibility of a cure. The panel realized there is extensive variability in clinical practice and outcomes that may correlate with where individuals live and receive care.

The panel also agreed that there are marked differences in the recommendation of HSCT for children compared with adults. The likely gains for children are also greater than for adults, if HSCT is successful. The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/oLT2VwqQTbM.

Conclusions. The panel determined that there is low certainty in the evidence that probably favors HSCT for patients with SCD and neurologic complications. Despite limited comparative data, it is likely that HSCT reduces the risk of new or recurrent ischemic stroke and SCI. The panel identified the following additional research needs: (1) research focused on patient values and preferences with regard to neurologic outcomes, and (2) research focused on neurologic outcomes and recovery after HSCT in those who had neurologic complications as an indication for HSCT.

Recommendation 2

Should individuals with frequent pain requiring interventions by a health care provider undergo matched related allogeneic transplantation vs standard of care?

Recommendation 2

For patients with frequent pain, the ASH guideline panel suggests using related matched allogeneic transplantation rather than standard care (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Consideration for transplantation should be given to patients who fail to respond or have an inadequate response to standard of care, such as hydroxyurea, new targeted therapies or chronic transfusion therapies.

Specific background. Individuals with SCD experience frequent and recurrent acute pain events that are the most common reason for acute care use. In addition, patients with frequent pain events requiring acute care use experience more morbidity and early mortality than those with less frequent acute care use.[41-43] Current treatments for prevention of these painful events may include the use of HU, CRCT, and oral L-glutamine or crizanlizumab, recently approved by the US Food and Drug Administration. In addition, HSCT has been used in patients with frequent painful events to prevent future episodes. The panel systematically reviewed the existing data and appraised the evidence to determine how allogeneic transplantation compares with the use of HU and CRCT to prevent recurrent acute pain events in patients with SCD.

Summary of the evidence. Studies were examined for the primary outcome of prevention of pain defined as ≥3 episodes of acute pain requiring intervention by a health care provider. The studies were also evaluated for the following additional outcomes: survival, engraftment, and acute and chronic GVHD. Twenty-two studies were identified from the literature in patients with SCD.[15,37,38,44-62] In general, sickle-related acute complications and RBC transfusions were

stopped in patients who experienced stable donor engraftment. Subsets of patients in each of the identified trials underwent HSCT because of recurrent pain. A majority of these studies focused their reporting on transplantation outcomes, and no studies compared HSCT with standard of care for the outcome of prevention of pain. When examining outcomes related to the prevention of pain post-HSCT, acute painful episodes requiring hospitalization were largely prevented when engraftment occurred. In addition, there was a limited amount of evidence that HSCT improved patient-reported outcomes relevant to pain in small subsets of patients. Darbari et al[44] described that patient-reported outcomes of pain intensity and pain impact were significantly improved post-HSCT in a subset of patients with only intermittent pain pre-HSCT. Saraf et al[47] in 2016 reported significant improvement in patient-reported bodily pain (measured by the SF36) 1 year post-HSCT. However, there are reports of patients still experiencing pain post-HSCT. Forty percent of patients post-HSCT had persistent pain requiring opioid medications at 1 year post-HSCT, suggesting that HSCT may not ameliorate chronic pain.[44] Further study of chronic pain and the impact of HSCT is needed, including longer-term follow-up post-HSCT for patients with SCD.

The studies were case series or single-arm prospective cohort studies. The systematic review did not find any comparative RCTs of patients with SCD. Because of this, using the GRADE process, when considering the certainty in the evidence, certainty was considered to be very low to moderate.

Benefits, harms, and burdens. The potential benefit of matched related allogeneic transplantation varies from small to moderate and includes prevention of acute pain events. The overall incidence of acute pain posttransplantation was found to be low to nonexistent. However, the differentiation of the occurrence of acute vs chronic pain events posttransplantation was difficult to ascertain from the published evidence, given the lack of standard chronic pain definition and lack of systematic reporting. In addition, the evidence for long-term benefits of transplantation, such as prolonged survival (eg, survival into adulthood for those undergoing transplantation in the pediatric years) and improved HRQOL, compared with standard of care, is lacking.

The risks of matched related allogeneic transplantation, including GVHD, infection, graft rejection, and infertility, are discussed in detail in recommendation 1. The additional risk of harm associated with this particular recommendation is the potential for chronic pain that is not entirely mitigated by HSCT.[44] Certain pain-inducing complications of SCD (eg, avascular necrosis) cannot be altered by transplantation. Additionally, individuals with SCD may develop a secondary chronic pain syndrome that is not directly improved by HSCT.[44] Thus, while acute pain events may be resolved, chronic pain may persist.

Rationale and key driver for recommendation. The balance between benefits vs harms may or may not favor HSCT for patients with SCD who experience frequent acute pain events. The overall certainty in the evidence of effects is very low because of (1) the lack of direct comparative RCTs of BM transplantation vs standard of care in SCD, (2) the relatively short-term follow-up and small sample sizes of the available studies, and (3) the lack of long-term well-defined patient-reported outcomes on pain after SCT.

Other EtD criteria and considerations. The benefit of prevention of acute pain in patients with SCD who undergo HSCT was felt to be a desirable effect that may balance the harms for some patients.

The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/pP1olBhxMyg.

Conclusions and research needs for this recommendation. The guideline panel determined there is overall very low certainty in the evidence for a net health benefit with regard to outcomes important to patients associated with HSCT in patients with SCD and frequent acute pain events. Despite the absence of comparative data of HSCT vs standard of care therapy in the prevention of acute pain in patients with SCD, HSCT is suggested given the observational data that demonstrate a strong effect on this outcome. The panel identified the following focus areas requiring research: (1) comparative studies of HSCT vs standard of care (eg, RCTs) that include standardized measures of pain pre- and posttransplantation, especially patient-reported outcomes, to determine the impact of the intervention on pain, (2) research to address the consequences of chronic opioid therapy in patients with SCD and how this may affect the resolution of pain post-HSCT, and (3) long-term follow-up studies of patients who have undergone matched related allogeneic transplantation to determine long-term benefits and risks related to this treatment. This includes monitoring for late effects, stratified by type of transplantation and age and including graft failure, organ function, and chronic pain.

Recommendation 3

Should matched related allogeneic transplantation vs standard of care be used for patients with SCD with recurrent episodes of ACS?

Recommendation 3

For patients with recurrent episodes of ACS, the ASH guideline panel *suggests* using matched related allogeneic transplantation over the standard of care (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Consideration for transplantation should be given to patients who continue to have recurrent ACS despite optimal standard of care (eg, HU, L-glutamine, crizanlizumab, and chronic transfusion therapy).

Specific background. Patients with SCD may experience recurrent episodes of ACS, which can be life threatening or fatal. ACS or progressive chronic lung damage is a leading cause of mortality in adults with SCD and poses a significant risk.[63] Patients with frequent ACS events also experience more morbidity. Current standard treatment of ACS prevention may include HU, CRCT, and oral L-glutamine, recently approved by the US Food and Drug Administration. In addition, HSCT has been performed in patients with ACS events to prevent recurrent episodes. The panel systematically reviewed the existing data for comparison of HSCT and standard treatment and appraised the evidence to determine how HSCT for SCD compares with HU and CRCT to prevent recurrent ACS events.

Summary of the evidence. Studies were examined for the primary outcome of ACS prevention and were selected if the indication for HSCT was explicitly stated as ACS events (recurrent or not). The studies were also evaluated for the following 3 additional outcomes: survival, engraftment, and acute and chronic GVHD. Sixteen studies were identified from the literature in patients with SCD.[15,38,45,47-49,51-53,56-58,60,64,65] Collectively, these studies demonstrate that ACS events no longer occurred in those cases where the HSCT procedure was successful. Additionally, some studies monitored lung function with pulmonary function tests post-HSCT. No worsening of pulmonary function was noted in these patients monitored post-HSCT; however, the follow-up period of most studies was limited (<5 years in most cases). Comparatively, the recurrence of ACS events was not eliminated with standard of care treatments, such as HU and CRCT. For patients treated with HU and CRCT, the reduction in ACS event recurrence varied from 71% to 92%.[66,67] Additionally, in a randomized phase 3 trial of the new L-glutamine agent, reduction in ACS was seen in ~63% of patients relative to those who received placebo.[68]

The HSCT studies reviewed were case series or single-arm prospective cohort studies. The systematic review did not find any comparative RCTs of HSCT vs standard of care therapies of patients with SCD. Because of this, using the GRADE process when considering the certainty in the evidence, certainty in the studies was considered to be very low to intermediate.

Benefits. The potential benefit of matched related HSCT was judged to be moderate and includes prevention of recurrent ACS events and stabilized pulmonary function test results.[69] The overall incidence of ACS post-HSCT was negligible or nonexistent after successful HSCT. However, the evidence for long-term benefits of HSCT, such as prolonged survival (eg, survival into adulthood for those undergoing transplantation as children), reduction of long-term chronic lung disease (eg, restrictive lung disease), and improved HRQOL compared with standard of care is lacking.

Harms. The harms of matched related allogeneic transplantation have been discussed in detail in recommendation 1. The potential for harm specific to this question is the inability to reverse some elements of chronic lung disease, such as restrictive lung disease. There are no specific associated harms thought to be relevant to this recommendation.

Rationale and key driver for recommendation. The balance between benefits vs harms may favor HSCT for patients with SCD who experience frequent or severe ACS events. The overall certainty in the evidence of effects is very low because of the lack of direct comparative studies and insufficient data on prolonged survival or reduction of preexisting or new-onset chronic lung disease for those who have undergone HSCT. However, the panel recognized that long-term survival outcomes are not improving in adults with SCD who receive standard of care therapy, and among adults, chronic pulmonary disease is prevalent and progressive and leads to higher mortality risk. In addition, transplantation-related harms are known to be worse in adults compared with children. The benefit of prevention of ACS in patients with SCD after successful HSCT was judged a desirable effect that may balance the harms in selected high-risk patients.

Other EtD criteria and considerations. In addition, the panel acknowledged there is no uncertainty in the benefit of prevention of ACS and that standard of care therapies such as HU can be very effective at prevention of ACS events for some patients. Decisions regarding patients' treatment preferences were acknowledged to be varied, where some patients may be ready to take any risk for the benefits of therapy, while others may not.

The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/GEEalX1nF1I.

Conclusions and research needs for this recommendation. The guideline panel determined there is overall low certainty in the evidence for a net health benefit in outcomes important to patients associated with BM transplantation in patients with SCD and frequent or severe ACS events. Despite the absence of comparative data of HSCT vs standard of care therapy in the prevention of ACS events in SCD, HSCT is justified in light of the observational data that demonstrate a strong effect on this outcome (ie, eliminates ACS after successful HSCT). The panel identified the following focus areas in need of research: (1) comparative prospective studies of HSCT compared with standard of care (eg, studies that include standardized measures of pulmonary complications pre- and post-transplantation, with a focus on patient-reported outcomes [eg, HRQOL and other functional outcomes], pulmonary function, and exercise capacity testing to determine the impact of the intervention on lung function), (2) research to address the pulmonary complications that would justify HSCT in patients with SCD, and (3) long-term follow-up studies in patients after matched related HSCT to determine long-term benefits and risks related to this treatment. This research includes monitoring for late effects stratified by type of transplantation and age and for graft failure and organ function.

Recommendation 4

Should individuals with SCD with an indication for SCT (as above) who do not have an MSD undergo nonmyeloablative transplantation from alternative donor vs standard supportive care?

Recommendation 4

For patients with SCD with an indication for HSCT who lack an MSD, the ASH guideline panel *suggests* using transplantation from alternative donors in the context of a clinical trial (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remark:

- Alternative donor transplantation has the potential to improve or resolve disease manifestations in patients with severe SCD. The risks related to transplantation complications should be balanced with benefits derived from a successful transplantation.

Specific background. Fewer than 20% of individuals with SCD have an HLA-matched sibling donor.[70] This observation has prompted alternative donor studies including HSCT with MUDs and haploidentical familial donors, often with reduced-intensity and nonmyeloablative regimens designed to achieve engraftment while reducing toxicity and late effects. For all these efforts, outcomes of prime importance include successful donor engraftment, low transplantation-related

complications such as GVHD and organ toxicity, successful immune reconstitution, and low mortality.

Summary of the evidence. Studies were examined for the primary outcomes of survival, graft failure/rejection, and acute and chronic GVHD as well as secondary outcomes of interest from recommendations 1 to 3 where appropriate. Alternative donor stem cell sources include MUD marrow, cryopreserved unrelated UCB products, and haploidentical familial donor stem cells. Because of the rather recent development of clinical trials of alternative donor HSCT for SCD, the number of transplantations reported for each stem cell source is small.

The systematic review summarized 17 small studies[45,52,53,71-84] to evaluate unrelated donor (marrow) HSCT, unrelated donor (cord) HSCT, and haploidentical familial donor HSCT. All of the initial alternative donor studies were discouraging, with a high incidence of graft rejection (in the unrelated UCB and most haploidentical trials) or GVHD (in the MUD and 1 pediatric haploidentical trial). More recently however, results have been much more encouraging, with decreased graft rejection and GVHD and improved survival. Since 2017, OS has been 79% to 100% and EFS 50% to 91% following alternative donor HSCT for SCD.[29,45,52,53,71-85] Details regarding organ toxicity and immune reconstitution are sparse. Results suggest these alternative donor options are increasingly successful.

Benefits. The number of patients receiving transplants from alternative donors is small and includes mostly children and young adults. The primary benefit is the ability to treat individuals with SCD with HSCT even if an MSD is not available. Early short-term follow-up after successful HSCT with alternate donors has demonstrated donor-derived hematopoiesis, correction of hemoglobin levels, successful cessation of chronic transfusion therapy averting an increasing iron load, control of pain episodes resulting in improved HRQOL, stabilization of CNS changes related to vasculopathy as demonstrated by cerebral imaging, and maintenance of IQ without the anticipated deterioration over time. The early benefits described above as well as long-term effects on other organ systems such as the lungs, kidneys, and gonads must be carefully tracked over time to define pros and cons for patients after successful alternative donor HSCT and to determine whether they align with benefits already established for MSD HSCT.

Harms. The toxicity burdens associated with alternative donor HSCT must be balanced with benefits in relation to mitigating the symptoms of SCD. The treatment-related toxicities that occur at high rates with alternative donor HSCT include graft rejection (in the unrelated UCB and early haploidentical trials) or GVHD (in the MUD and 1 pediatric haploidentical trial). Data on immune reconstitution and susceptibility to infection as well as regimen-related organ toxicity have not been well documented. Mortality has been higher than with MSD HSCT when considering all alternative donor HSCTs together; however, more recent results have been much more encouraging, with decreased graft rejection and GVHD and improved survival, especially in the haploidentical setting. However, because alternative donor HSCT was initiated more recently, less is known about potential harms and late complications because of the smaller number of patients undergoing transplantation and shorter duration of follow-up (as compared with MSD HSCT).

Rationale and key drivers for recommendation. The balance between benefits vs harms may favor HSCT with alternative donors for patients with severe SCD only within the context of a clinical trial. The overall certainty in the evidence of effects is very low because of the lack of current available data and long-term follow-up. However, the panel recognized that the benefits associated with a potential cure, which include potentially slowing or even improving the organ dysfunction that occurs as patients with SCD age and improving HRQOL, may outweigh concerns about increased risks associated with alternative donor HSCT, particularly in the context of clinical trials where eligibility criteria are selected to restrict this intervention to patients with severe SCD and ensure detailed posttransplantation monitoring.

Other EtD criteria and considerations. The panel agreed that after alternative donor HSCT, there is a potential for decreased interruption of work/school/activities if patients remain transfusion and hospitalization independent and organ function is stabilized. The eligibility criteria for alternative donor HSCT studies may be more stringent because of the potential for increased risk. Furthermore, the nonmyeloablative conditioning or RIC commonly used in the alternative donor setting may allow consideration of HSCT in patients with more severe disease manifestations and end organ damage. The panel recognized that this is a group of patients likely to have increased health care use and poor QOL (because of SCD) and may benefit more from successful HSCT than less severely affected individuals. The panel agreed that there may be important uncertainty or variability in how much patients and families value a cure in the context of increased potential risks and fear of the unknown as compared with standard treatment measures. The panel found significant variability in acceptance based on the patient's social situation and physician practice. The panel also agreed that there are significant differences in the recommendation of HSCT for children, adolescents, and adults because of inherent risks from HSCT associated with patient age, disease status, and expected longevity.

The complete EtD framework for this question, including evidence tables, is available at https://gdt.gradepro.org/app/handbook/handbook.html.

Conclusions and research needs for this recommendation. The guideline panel concluded that there is very low certainty regarding nonmyeloablative or reduced-intensity alternative donor HSCT for patients with SCD. All reports are short-term descriptions and have variable outcomes. As was observed in the MSD HSCT setting, most studies with alternative donors report only on transplantation outcomes such as survival, engraftment, and GVHD, but not on disease-specific outcomes. Additional studies must assess long-term effects of HSCT on disease-specific outcomes with regard to age, stem cell source, transplantation approach, degree of HLA matching, stability of donor cell engraftment and level of chimerism, and degree of organ stabilization or improvement.

Recommendation 5

Should allogeneic transplantation with TBI-based regimens (low-dose TBI ≤400 cGy) vs chemotherapy-based regimens be used for patients undergoing allogeneic transplantation for SCD?

Recommendation 5

For allogeneic HSCT, ASH guideline panel *suggests* using either TBI ≤400 cGy or chemotherapy-based conditioning regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Specific background. Chemotherapy-based conditioning with busulfan and cyclophosphamide, with or without serotherapy with antithymocyte globulin, represents the standard of care for pediatric patients with SCD undergoing MSD HSCT. Although highly effective in children, this regimen limits access for a large fraction of adults with severe disease and other comorbidities given the greater potential for toxicity in the population of adults with SCD. As the management of pediatric patients has improved, many are delaying the decision regarding HSCT until adulthood, when the disease burden increases. To address this in the adult population, nonmyeloablative regimens based on low-dose TBI have been developed and seem highly effective in reversing the disease. However, the long-term effects of irradiation remain a concern, and there have been no direct comparisons of these conditioning regimens in a prospective randomized trial.

Summary of the evidence. Studies were examined for the primary outcomes of survival, graft failure/rejection, and acute and chronic GVHD; secondary outcomes of interest from recommendations 1 to 3 where appropriate; and risk for malignancy and potential for fertility post-HSCT. No studies were identified that directly addressed the long-term effects of low-dose TBI in the setting of allogeneic HSCT for SCD. In 1 report,[86] there were no late malignancies described among 30 patients with SCD conditioned with low-dose TBI; however, the follow-up was brief. Additionally, there were case reports describing malignancies (eg, myelodysplastic syndrome and acute leukemia) in patients with SCD after undergoing allogeneic transplantation with chemotherapy-based regimens[87] and low-dose TBI-based regimens[88,89] and in the absence of transplantation,[87,90] making attribution difficult. Only 1 report described the assessment of fertility after low-dose TBI in 31 patients and noted no effect on the hypothalamus-pituitary-adrenal axis and no effect on male gonadal function (male participants underwent testicular shielding). Female participants had evidence of SCD-related reduced ovarian function before transplantation, which worsened with transplantation. Three natural pregnancies were described in 2 women, demonstrating fertility preservation is possible after low-dose TBI.

Benefits, harms, and burdens. The major benefit of low-dose TBI-based conditioning is the potential for fertility preservation, which was viewed by the panel as significant. However, this was based on 1 published report with a limited sample size. Although not definitive, there is a concern that fertility-sparing regimens based upon low-dose TBI may be associated with a risk of myelodysplastic syndrome/acute leukemia that is higher than that associated with regimens based upon myeloablative chemotherapy. As such, the benefit of fertility preservation may come with an increased risk of this complication. However, the limited data currently in the literature are insufficient to assess the potential benefits and burdens of the 2 approaches with respect to the outcomes.

Rationale and key drivers for this recommendation. The balance of benefits vs harms favors neither low-dose TBI nor chemotherapy-based conditioning regimens for patients undergoing allogeneic transplantation for SCD. There were no specific studies found to address the concerns of long-term effects of low-dose irradiation in the context of allogeneic transplantation. However, we identified case reports of myelodysplastic syndrome/acute leukemia in patients with SCD after both chemotherapy-based and low-dose TBI-based regimens along with reports of an increased incidence of myelodysplastic syndrome/acute leukemia in patients with SCD who had not undergone transplantation, demonstrating the need for long-term follow-up studies. We identified a report of preservation of fertility with the low-dose TBI approach.

Other EtD criteria and considerations. The panel noted that the improved management of children with SCD has shifted the consideration of HSCT for many into adulthood. The anticipated toxicity of myeloablative conditioning in adults with accumulating organ damage has prompted the development of nonmyeloablative transplantation with low-dose TBI to enable HSCT in this population. Patients and their families place a high value on the option for curative therapy in adults afforded by this approach. Patients and their families also place a high value on reproductive fitness, and the infertility associated with myeloablative conditioning is a concern that has historically limited the acceptance of myeloablative conditioning and transplantation in SCD. The panel also agreed that there may be possibly important uncertainty or variability in how much people value the outcome of a successful HSCT when compared with the limited long-term data on the possible risks of TBI compared with chemotherapy-based conditioning.

The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/JV5JRlUUhfs.

Conclusions and research needs for this recommendation. The guidelines panel made a conditional recommendation based on very low certainty because of the absence of sufficient/good/valid data in the literature. Further research is warranted, including registry analyses that are conducted at long-term follow-up comparing outcomes based upon transplantation conditioning. Furthermore, fertility in SCD has not been well studied outside of the field of transplantation, and efforts to characterize the effects of SCD on fertility are warranted. Detailed assessments of fertility prior to transplantation and during extended follow-up are also warranted. This will allow patients to make better-informed decisions on whether to pursue transplantation and, if differences between regimens are established, choose a regimen that reflects the proper balance of competing benefits and burdens.

Recommendation 6

Should individuals with SCD and an indication for HSCT (as above) and an MSD receive myeloablative conditioning, RIC, or nonmyeloablative conditioning?

Recommendation 6a

For children with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* using myeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 6b

For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* nonmyeloablative conditioning over RIC that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Specific background. Although HSCT has curative potential in SCD, outcomes for the subgroup of children younger than 16 years of age undergoing MSD HSCT are better compared with those for adults. Adults with SCD are more likely to have accumulated disease-related morbidities, which may limit their ability to participate in HSCT. To optimize outcomes in both children and adults, alternative conditioning regimens that include reduced-intensity or nonmyeloablative approaches must be explored. Unfortunately, there have been no direct comparisons of these conditioning regimens in a prospective randomized trial controlling for type of donor and indication for transplantation. Therefore, there is very low certainty in the evidence supporting the recommendations that follow.

Summary of the evidence. Studies were examined for the primary outcomes of survival, graft failure/rejection, and acute and chronic GVHD; secondary outcomes of interest from recommendations 1 to 3 when appropriate; and potential for fertility post-HSCT. The panel was unable to find any study that directly compared outcomes in children or adults undergoing HSCT using myeloablative vs either RIC or nonmyeloablative conditioning. However, the committee evaluated data from the CIBMTR and addressed the comparison of interest among common conditioning regimens administered in HSCT.[29]

This registry data included a cohort of 910 patients who underwent HSCT by MSD, unrelated donor, and HLA-haploidentical family donor. Myeloablative conditioning was busulfan based, and nonmyeloablative conditioning consisted of low-dose TBI with in vivo T-cell depletion. RIC regimens, analyzed as a single group, consisted almost entirely of a combination of melphalan/fludarabine with or without thiotepa. The predominant conditioning regimen was myeloablative in 348 (62%) of 558 transplantions with an HLA-matched sibling donor. EFS was superior in those younger than 13 years of age. There was no significant difference in EFS between recipients of transplants from nonsibling donors. Conditioning regimen intensity was not associated with survival after HLA-identical sibling HSCT. However, graft failure was higher after RIC compared with myeloablative (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.13-0.57; $P < .0001$) and nonmyeloablative (HR, 0.29; 95% CI, 0.08-1.00; $P = .049$) regimens. EFS also was lower after RIC compared with myeloablative (HR, 0.38; 95% CI, 0.21-0.67; $P = .00080$) and nonmyeloablative (HR, 0.36; 95% CI, 0.13-0.94; $P = .036$) regimens. The rate of chronic GVHD was highest in patients treated with myeloablative regimens, less high in those receiving RIC regimens, and lowest in those receiving nonmyeloablative conditioning regimens. When OS is compared across all regimens (myeloablative, reduced intensity, and nonmyeloablative), nonmyeloablative conditioning has the highest survival advantage a large part because of the lower rate of chronic GVHD. Therefore, a nonmyeloablative regimen is recommended over RIC in older patients, because the HR for EFS was significantly higher (1.00 vs 1.97; 95% CI, 1.15-3.36; $P = .013$).

Benefits. Potential benefits associated with a nonmyeloablative preparative regimen include a reduced risk of mortality and GVHD in adults after HSCT, although EFS does not seem to be different after myeloablative and nonmyeloablative regimens.

Harms. Potential harms of myeloablative conditioning, including risk of infection and infertility (Table 3), were previously discussed. Additional potential harms associated with RIC regimens that rely upon a combination of melphalan/fludarabine include inferior EFS. Another potential harm is the increased risk of graft failure associated with RIC regimens. Therefore, regimens using RIC must be individually evaluated for outcomes and risks to provide better comparisons of myeloablative and nonmyeloablative regimens.

Rationale and key driver for recommendation. The guideline panel determined that there is very low certainty in the evidence for a net health benefit vs harm from using a nonmyeloablative or reduced-intensity regimen over a myeloablative regimen. The strength of the recommendations is weakened by the retrospective nature of the studies examined for comparison of outcomes. In addition, the decision to pursue HSCT, the timing of HSCT, the choice of conditioning regimen intensity, and the choice of an optimal alternative donor when there is no sibling donor were not controlled for or considered in these comparisons.

Other EtD criteria and considerations. The panel considered the potential for improved survival in adults receiving a less intensive chemotherapy regimen. The panel acknowledged that the availability of TBI may depend on treatment center and geographic location. The panel also acknowledged that myeloablative regimens may result in higher transfusion requirements and other supportive care measures.

The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/WISE0dFCFEM.

Conclusions and research needs for this recommendation. The panel concluded there is very low certainty in the evidence supporting these recommendations. The panel identified extensive additional research needs for these recommendations. Additional follow-up and investigation of the risk of treatment-related malignancies after nonmyeloablative conditioning regimens should be pursued. These data should be systematically analyzed. It is also recommended by the panel that conditioning regimens for HSCT for SCD should be compared in prospective clinical trials.

Recommendation 7

Should age be a determining factor for HSCT with MSD for individuals with SCD with the above indication?

Recommendation 7

In patients with an indication eligible for HSCT, the ASH guideline panel *suggests* using allogeneic transplantation at an earlier age rather than an older age (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

- Recommendations could not be made if an MSD was not available because of the paucity of available data.
- The impact of age on HSCT outcome also may be affected by the conditioning regimen used.

Specific background. It is well documented that SCD complications accrue with age. Certain complications resulting in tissue death

such as avascular necrosis and ischemic stroke cannot be reversed by HSCT. Therefore, it is necessary to assess if individuals with SCD should undergo HSCT at an earlier age or if the benefits of HSCT will still be valuable at later ages.

Summary of the evidence. Studies were examined for the primary outcomes of survival, graft failure/rejection, and acute and chronic GVHD as well as secondary outcomes of interest from recommendations 1 to 3 where appropriate. Given the absence of studies that directly compared outcomes in younger vs older patients with SCD undergoing HSCT using an MSD, the panel examined data from CIBMTR. In that study, EFS was highest in children younger than age 13 years and with an MSD.[29] Patients older than age 13 years had not only lower EFS (HR, 1.74; $P = .0014$) but also lower OS (HR, 3.15; $P < .0001$) and higher chronic GVHD risk (HR, 1.46; $P = .019$). However, the impact of age on outcomes is also dependent on the type of HSCT. With myeloablative conditioning, the risk of chronic GVHD is significantly higher in those older than 15 years of age. In contrast, these findings may be mitigated with nonmyeloablative conditioning.[91] Several recent studies of HSCT in adults using nonmyeloablative conditioning demonstrated no chronic GVHD or associated transplantation-related mortality. EFS was only 87%, because 13% had graft rejection.[46,82,86]

Benefits. The anticipated benefits of transplantation at a younger age could be large and include lower GVHD risk and decreased transplantation-related mortality as well as improved EFS with less graft rejection. Additional benefits might include the preservation of organ function as a result of HSCT being performed before there were substantial SCD-related organ complications.

Harms of HSCT include risk of infection, GVHD, graft rejection, risk of secondary malignancy, and infertility. However, these harms affect individuals with SCD of all ages undergoing HSCT. No current studies have found additional harms secondary to performing HSCT in younger individuals with SCD. The harms related to HSCT continue to depend mostly on the type of transplantation conditioning used.

Rationale and key driver for recommendation. The balance between benefits vs harms in early transplantation probably favors transplantation at a younger vs older age but may be influenced by the presence of an MSD and the severity of the disease. However, the overall certainty of effects is low given the lack of prospective studies that directly compare HSCT outcomes by age. Nonetheless, early transplantation with an MSD is associated with reduced GVHD, lower transplantation-related mortality, and higher OS. Transplantation at an earlier age may also help preserve organ function. These benefits, however, should be balanced against the potential for harm from transplantation-related toxicity and mortality risks, which are never nonexistent.

Other EtD criteria and considerations. The panel also valued the likelihood of improved HRQOL and lifetime health-related cost savings associated with successful HSCT at a younger age given the known natural history of SCD.

The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/eWAQORgWjrw.

Conclusions and research needs for this recommendation. The panel determined there is a low certainty in the evidence for the net benefit of transplantation at a younger vs older age in patients with SCD and an MSD. However, the panel believed that a conditional recommendation was justified because of the ability to use myeloablative regimens in younger patients, the preservation of organ function prior to SCD-induced damage, and the likely cost saving. However, for those without an MSD, the recommendation is not as strong, because the data are not sufficiently mature.

The panel identified the following areas of research that are needed: (1) long-term comparative studies (SCT vs standard care) stratified by complications and randomized by donor availability, such as the recently reported[39] DREPAGREFFE trial for children with abnormal TCD and the ongoing BMT CTN 1503 trial, and (2) retrospective studies comparing long-term effects depending on age at transplantation, such as gonadal function, fertility, and risk of malignancies.

Recommendation 8

In pediatric patients with SCD, an indication for BM transplantation, and available cryopreserved matched sibling cord blood, should myeloablative BM transplantation be used vs myeloablative cord blood transplantation?

Recommendation 8

The ASH guideline panel *suggests* the use of HLA-identical sibling cord blood when available (and associated with an adequate cord blood cell dose and good viability) over BM (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Specific background. Since 1988, UCB has been successfully used as a source of stem cells for hematopoietic reconstitution in allogeneic HSCT. For patients with SCD, it is possible to propose and organize the systematic cryopreservation of cord blood collection from full siblings born after the patient with SCD. However, the benefit/risk balance of using cord blood vs BM from an MSD for a child with SCD and an indication of HSCT is not well understood.

Summary of the evidence. Studies were examined for the primary outcomes of survival, graft failure/rejection, and acute and chronic GVHD as well as secondary outcomes of interest from recommendations 1 to 3 where appropriate. There were 3 main studies that reported retrospective comparisons of outcomes after UCB vs BM transplantation in patients with SCD. The study by Locatelli et al[92] evaluated individuals with all types of hemoglobinopathies and included those with SCD (UCB, n = 30; BM, n = 130). In a similar study, Bernaudin et al[91] reported the comparison of 30 UCB vs 195 BM transplantations in patients with SCD, and a recent report by CIBMTR compared outcomes of 34 UCB vs 311 BM transplantations.[29]

These studies reported a significantly longer median time to neutrophil and platelet recovery after HSCT with a UCB donor when compared with BM donor, but without a significantly increased risk of infections or risk of nonengraftment. There were no deaths observed after UCB transplantation, and there was a trend toward lower acute and chronic

GVHD after UCB transplantation. OS and EFS were similar for all cell sources.

Benefits. The benefit of cord blood is based primarily on the lower risk of GVHD associated with using cord blood. However, the certainty in the evidence for effects was very low, because the patients receiving UCB were usually younger than those receiving BM and therefore at lower risk of GVHD regardless of cell source. Furthermore, these were retrospective studies that did not directly compare other outcomes of interest (eg, organ function). Finally, OS is similar in both groups. One additional potential benefit associated with using UCB is the avoidance of donor risk/attrition, because cord blood collection is without risk to the donor (ie, no requirement for general anesthesia or harvest procedure).

Harms and burdens. Harms associated with UCB transplantation include the longer time to engraftment and therefore increased risk for infection. This significantly longer recovery time for neutrophils and platelets does increase the supportive care burden and the burden of potential discomfort on the patient; however, this burden did not translate into inferior overall outcomes. Additionally, it is difficult to balance the differences in efficacy with the risk of GVHD, because these trials were not randomized. Despite the nonsignificance in OS,[14,91,92-96] it is important to note that no deaths were observed after HSCT with UCB.

Rationale and key drivers for recommendation. The balance between benefits vs harms probably favors UCB over BM for children undergoing HSCT using an HLA-identical sibling based primarily on decreased GVHD risk. However, the overall certainty in the evidence is very low, because there are no RCTs to directly compare UCB with BM HSCT, and additional information is needed to assess EFS. However, given the information available, the panel felt the current evidence favors UCB over BM when there is a choice of stem cell product. It is also important to discuss UCB HSCT with families of affected children who are considering having additional children. With this information, families can opt to organize UCB cryopreservation in case the new sibling is an HLA match.

Other EtD criteria and considerations. There are different costs incurred between the different procedures, with cryopreservation and storage of UCB potentially having a higher cost than BM harvesting. Considering the successful use of UCB HSCT in patients with SCD, in vitro fertilization combined with preimplantation genetic diagnosis could increase access to MSD HSCT. However, feasibility and high costs limit the usefulness of this therapeutic strategy. Furthermore, the ethical decision to have a child to serve as a UCB donor also warrants discussion if considering this option. Finally, there might also be a benefit of combining a marrow harvest with UCB when the cord blood cell dose is judged too small to support engraftment but could still be used to reduce risk of GVHD, although this has not been well studied.

The complete EtD framework for this question, including evidence tables, is available at https://guidelines.ash.gradepro.org/profile/yATgrmb9xE4.

Conclusions and research needs for this recommendation. The panel determined that there is very low certainty in the evidence for a net benefit related to using UCB over BM. The panel can only expect that with an increasing use of UCB HSCT, it will be possible to better determine the GVHD risk and OS/EFS compared with BM HSCT. The panel can only conclude that for SCD children with cryopreserved HLA-identical UCB, UCB HSCT offers a lower risk of GVHD (provided a sufficient cell dose is available) and that UCB may be combined with BM from the same donor with excellent results when UCB dose is limited.[97,98] The panel identified the following additional areas of research that are needed: (1) studies comparing SCD-related complications (eg, neurologic complications, pain crisis, and ACS) and HRQOL after UCB vs BM transplantation, (2) studies evaluating the relative risks of opportunistic infection, hospital days, and resource use after UCB vs BM transplantation, (3) studies comparing the acceptability of UCB vs BM transplantation among the various stakeholders (patients with SCD, parents, care providers, and others), and (4) research regarding cord blood HSC expansion to enable both improved recovery time for neutrophils and platelets and extension to older/larger recipients.

Good practice statements for HSCT

1. Providers and health care centers that offer allogeneic HSCT to patients with SCD should ensure that potential patients have been seen and counseled by an SCD specialist in addition to a specialist in HSCT to review all available treatment options.
2. Providers and health care centers that offer allogeneic HSCT to patients with SCD should be adequately trained in the specialized care required by such patients, including supportive care, which differs from that of other disease states.
3. Disease and transplantation-related outcomes should be monitored in the short (<2 years) and long term (10-15 years) in all patients after HSCT for engraftment, SCD symptoms, organ function, GVHD, transplantation-related complications, secondary malignancies, and (for patients undergoing alternative donor HSCT) immune reconstitution.
4. Care providers should consider health literacy levels of patients and their families when advising on HSCT.
5. Care providers should consider the burdens of the HSCT procedure on patients and their families.
6. Shared decision making between patients and providers is suggested to establish optimal HSCT plans.

Conclusions

The use of HSCT for SCD is evolving. The evidence for all recommendations is of low or very low certainty because of the lack of RCTs for HSCT in SCD, the lack of universal end points used in HSCT trials, and the lack of direct comparative therapies. The conditional nature of the recommendations for all questions results from the short duration of accumulated data and the reliance on evaluation of noncomparative data. MSD HSCT should be considered for all individuals at risk of neurologic injury or with recurrent vasoocclusive pain crises or a history of recurrent ACS. Furthermore, when feasible, the panel agreed HSCT should be undertaken at the earliest age possible. However, given the benefits and burdens of HSCT, the panel expressed strong views that all patients (even those without an MSD) with severe complications of SCD (indications for transplantation as above) should

receive information about transplantation as an option. For adults with SCD, undergoing HSCT with an MSD and nonmyeloablative therapy is recommended. Overall, alternative donor HSCT and newer nonmyeloablative regimens should be undertaken in the context of a clinical trial to better evaluate the efficacy and outcomes for future recommendations.

Further research needed

These guidelines are clearly limited because of the low certainty in the evidence. There are many reasons that evidence is lacking, and there are several recommendations offered to improve upon the existing recommendations.

Need for a clinical longitudinal registry

To fully realize the benefits vs harms assessment in HSCT for SCD, it is first necessary to better characterize the current natural history of SCD. Therefore, it is necessary to establish registries for both patients who undergo transplantation and patients who do not. It is highly important that a selected registry platform be validated, easy to access, and highly accessible to all SCD centers. It is also imperative that centers agree on which registry will be used and identify end points that can be tracked longitudinally and compared between those undergoing and not undergoing HSCT and are biologically relevant. This is especially important because it is highly difficult to justify comparative head-to-head studies that have transplantation as the intervention compared with standard of care. Although these are needed to optimally assess outcomes, such as long-term survival, long-term morbidity, organ function, and secondary malignancy, these are difficult to undertake. There are significant difficulties/challenges involved with the implementation of RCTs comparing an already proven curative approach with noncurative approaches, including the ethical challenges posed by the withholding of a potentially curative therapy. As such, RCTs that properly address all of the gaps in our knowledge are unlikely.

Increased access to care by SCD specialists for individuals living with SCD

Optimal implementation of HSCT will need to consider access to an SCD specialist, access to a transplantation center, compliance, and social, financial, and logistic support. HSCT is likely cost effective. Comparison of high-risk SCD adults who underwent HSCT using a nonmyeloablative conditioning regimen vs those referred for HSCT who did not proceed because of lack of an HLA-matched sibling donor, denial by insurance, anti-HLA antibodies to the potential donor, excessive RBC antibodies, or decision to decline further evaluation suggested that allogeneic HSCT leads to improvements in health care use and costs.[99] An assessment of cost effectiveness in other types of patients and types of transplantation with regard to long-term outcomes remains necessary.

Furthermore, indications for HSCT must balance the increased risk of toxicities in all transplantation settings to ensure that potential benefits outweigh the risks and must be considered in the context of disease burden with time and advancing patient age and the influence of supportive care.

The ASH panel recommends the following: (1) at least 5 years of follow-up and, if feasible, even longer-term follow-up for assessment of transplantation-related complications and long-term efficacy and monitoring of patient-reported outcomes, organ function, and longevity (registry studies could be beneficial with regard to long-term follow-up), (2) development of cohort studies for systematic tracking, (3) uniform tracking methods between HSCT protocols, and (4) outcome measures specific to HSCT and SCD. Research priorities should include education regarding HSCT as a potential treatment option for eligible patients and optimization of details of follow-up parameters and duration. It is therefore important for patients with SCD undergoing HSCT, especially those who undergo nonmyeloablative and/or alternative donor HSCT, to be enrolled in clinical trials, and it is important that funding be made available to support this potentially curative intervention as well as to support long-term follow-up.

Enhanced evaluation of newer disease-modifying therapies and their impact on quality and length of life for those living with SCD

There are new potentially disease-modifying medications (eg, L-glutamine, crizanlizumab, and voxelotor) that have recently been approved in the United States for SCD and ongoing development of additional therapies both for new medical treatments and for HSCT (eg, gene therapy). It is unclear how these newer therapies will affect SCD outcomes, including organ complications, and if broader access to a curative therapy will alter the trajectory of SCD outcomes. It is possible that new recommendations will be needed once long-term data are assembled on these newer agents.

Immense need for predictive biomarkers of mortality in SCD

SCD is highly variable. Although several different blood and urine biomarkers have been described in SCD, there are likely additional genomic and environmental modifiers of disease that have not yet been evaluated. Many of these biomarkers are organ specific (eg, microalbuminuria or proliferative retinopathy), whereas others are more global indications of SCD (eg, hemolysis, inflammation, and hypercoaguability). Furthermore, many of the identified biomarkers are abnormal in the steady state and become increasingly abnormal during acute vasoocclusive episodes, complicating measurement. Despite this knowledge, it is not clear that any current biomarkers provide specific prognostic or clinical information beyond the acute period or can be prognostically used in children to suggest or predict mortality when they become adults, preventing their use in HSCT. Thus, the identification of prognostically validated biomarkers in additional to a longitudinal clinical registry could greatly enhance the field of SCD treatment.

Updated data needed to evaluate newer alternative donor transplantation regimens

Updated data are needed to assess newer regimens such as haploidentical transplantation and add to this literature. These data must include all of the relevant outcome data so that comparisons across donor types can be performed. Additionally, these data must be collected across newly evolving curative therapy approaches, such as those involving gene disruption for fetal hemoglobin reactivation or gene correction using genome editing and addition tools.

What are others saying, and what is new in this ASH guideline?

To date, the only other official guideline on the use of HSCT in SCD was developed by the European Blood and Marrow Transplantation

Inborn Error Working Party and the Pediatric Disease Working Party and published in 2014.[100] The committee panel included 20 members with clinical and scientific expertise in HSCT and/or medical management of SCD. That guideline also used the GRADE approach as above. Patient stakeholders were not included in the working groups. They recommended that children with symptomatic SCD who have an HLA-matched sibling donor undergo SCT, consistent with recommendations 1 and 2 from this panel.[14] In contrast, they are more liberal in their recommendations for unrelated donor HSCT, stating more strongly that a transplant from an unrelated donor should be considered if a patient has at least 1 major organ-related complication or recurrent pain episodes. They do suggest that unrelated donor transplantation only be undertaken as a controlled trial in an experienced center as per the recommendations in this guideline. This panel did not fully endorse this recommendation, because there are no long-term data to support HSCT for certain organ complications, such as renal nephropathy and lung disease. For patients with neurologic indication or recurrent pain episodes or ACS, their recommendations parallel those in this document.

Limitations of this guideline

The limitations of this guideline are inherent to the low or very low certainty in the evidence we identified for many of the questions. In these cases, the panelists judged that patients who choose the suggested intervention would likely be better off than those who do not. As is clearly written, our recommendations are not intended for standard of care but rather for people seeking these specific therapies. Please note that the panel suggested multiple areas of important future research and emphasized the importance of shared decision making.

The recommendations are consistent with the GRADE approach, which allows for recommendations even in situations of low certainty in the evidence. It could be argued that recommendations and guidelines such as these are often more important when the certainty in evidence is very low, compared with when there is high certainty. The panel made these recommendations with the best judgment of the evidence (although scant), information about the disease, and relevant contextual factors.

Revision or adaptation of the guideline

Plans for updating the guideline

After publication of this guideline, ASH will maintain it through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of this guideline will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[101]

Acknowledgments

The authors thank Joi Williamson for her important contribution; Starr Webb, Robert Kunkle, and Kendall Alexander from ASH for their assistance with coordination of the guideline development effort; Mary Eapen from the Center for International Blood and Marrow Transplant Research (CIBMTR) for access to CIBMTR data that were helpful in our deliberations; and Lubna Daraz, Jehad Almasri, Bradley Beuschel, Larry Prokop, and Zhen Wang from the Mayo team for data extraction.

J.A.P. contributed to this article as an employee of the Medical College of Wisconsin. The views expressed are her own and do not necessarily represent the views of the National Institutes of Health or the US Government.

Authorship

Contribution: J.K. and J.T. wrote the first draft of the manuscript and revised the manuscript based on authors' suggestions. Guideline panel members R.I.L., F.B., J.B.-M., C.D.F., J.S.H., M.H.M., J.A.P., D.R., S.S., J.W., M.C.W., T.W., and J.J.M. critically reviewed the manuscript and provided additional information. M.H.M. led the evidence synthesis process and provided methodology support. J.T. and J.J.M. were the co-chairs of the panel and led the panel meeting. All authors approved the content.

Conflict-of-interest disclosure: All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure of interest form, which was reviewed by ASH and is available in supplements 2 and 3.

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