Overview of the 2020 ASH guidelines for transfusion support in SCD

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Clinical Guidelines

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

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CLINICAL GUIDELINES

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

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

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

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

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

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

Summary of recommendations

Background

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

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

How were these ASH guidelines developed?

PANEL FORMATION

Each guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

10 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

Example: PICO question

"Should automated red cell exchange vs simple transfusion or manual red cell exchange be used for patients with SCD receiving chronic transfusions?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

What do these guidelines cover?

- 10 recommendations focused on red cell antigen typing and matching, indications and mode of administration (simple versus red cell exchange), as well as screening, prevention and management of alloimmunization, DHTRs and iron overload
- 9 recommendations were conditional
  - paucity of direct, high-certainty evidence for outcomes of interest
- Several recommendations have moderate resource implications given the cost of transfusion and the requirement for exchange transfusion in certain patient scenarios

How can we prevent alloimmunization and delayed hemolytic transfusion reactions?

Recommendation on red cell antigen typing

The panel suggests an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally prior to first transfusion) *(conditional recommendation, very low certainty in the evidence about effects)*

- Includes C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s at a minimum
- Red cell antigen profiles should be made available across hospital systems
- A serologic phenotype may be inaccurate if transfused in the past 3 months
- Genotyping is preferred for the additional antigen information and increased accuracy for, among other things, C antigen determination and Fyb antigen matching

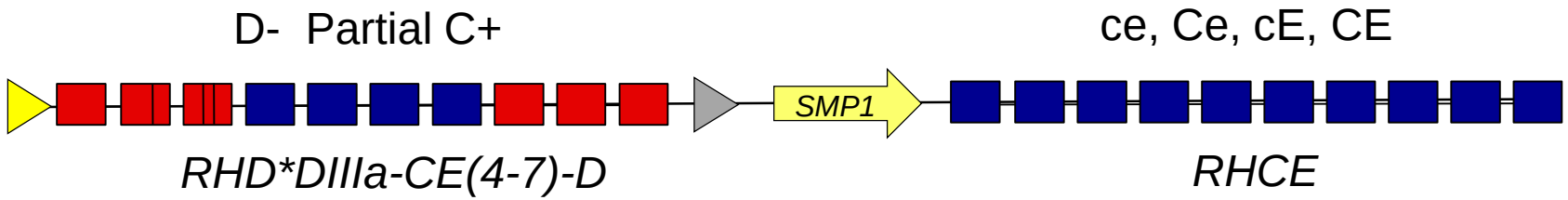
Rationale

The extended red cell antigen profile

- Needs to be performed only once
- Reduces alloimmunization when used to antigen match patients with blood donors
- Expedites antibody identification and aids donor unit selection when a patient requiring transfusion presents with a positive antibody screen

Genotyping assays for blood group antigens

- Extended red cell antigen profile
  - Human Erythrocyte Antigen (HEA) provides DNA predicted status on > 30 antigens, and is FDA-approved test of record
  - Identifies the "GATA" mutation in *DARC* gene that results in loss of Duffy antigen expression, specifically in red cells
- Higher resolution or comprehensive *RH* genotyping that identifies Rh variants
  - Hybrid *RHD*DIIIa-CE(4-7)-D* allele
  - Type C+ with common serologic assays
  - Prophylactic C- units indicated if no conventional RHCE*Ce or *CE



Recommendation on red cell antigen matching

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

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

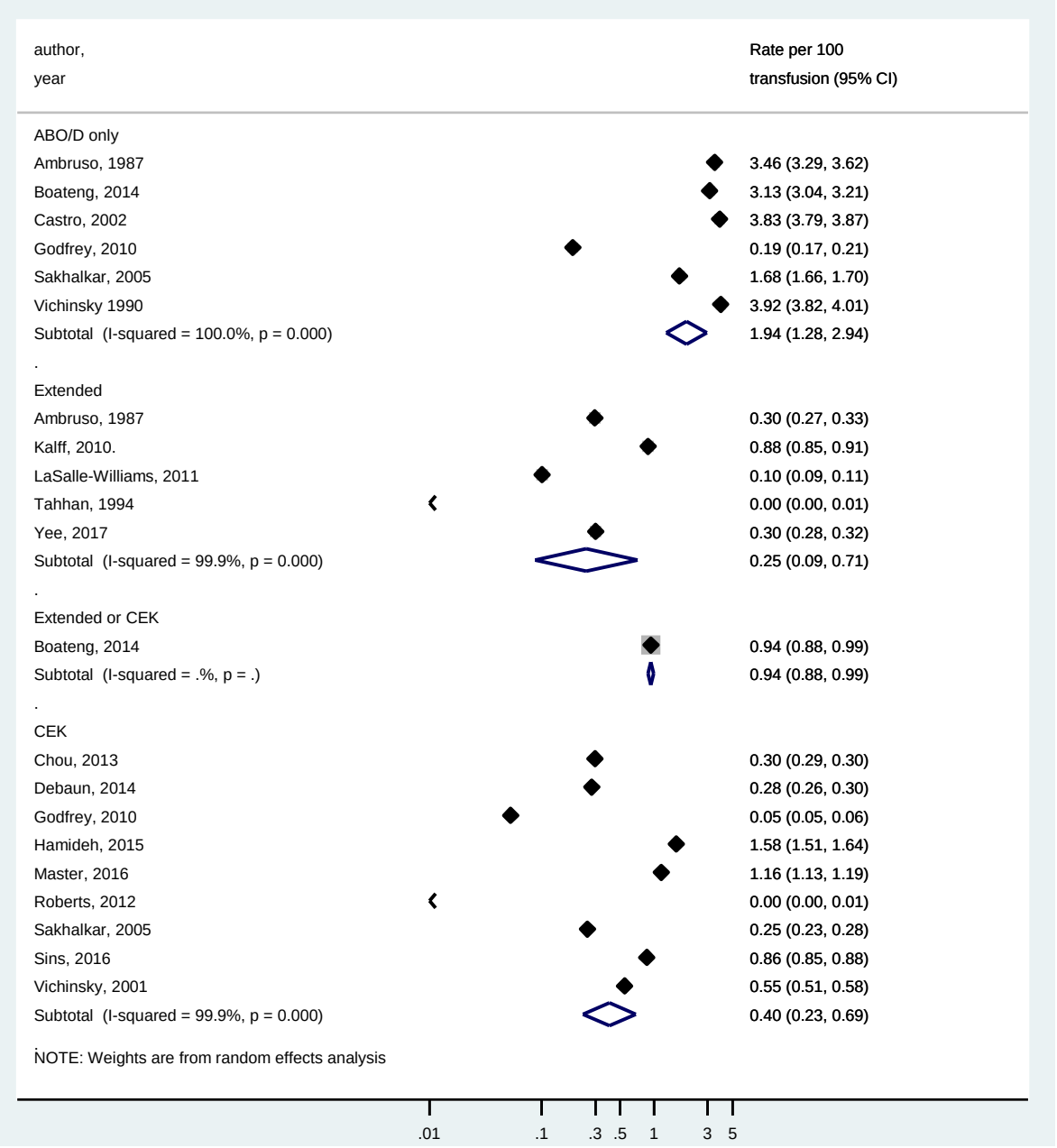
Rationale

- Alloimmunization incidence in patients with SCD is the HIGHEST of any transfused patient population
- Transfusion burden, inflammation, and *RH* genetic diversity play a role
- Prevention of antibody formation may avoid hemolytic transfusion reactions, difficulty in identifying sufficient antigen-negative units and transfusion delays

Evidence

When the data were pooled from single arm studies, a significantly lower alloimmunization incidence rate was noted with Rh, K or extended matching vs. ABO/D matching alone:

- Rh (C/E or C/c, E/e) and K matched: **0.40** per 100 units transfused
- Extended matched: **0.25** per 100 units transfused
- ABO/D matched: **1.94** per 100 units



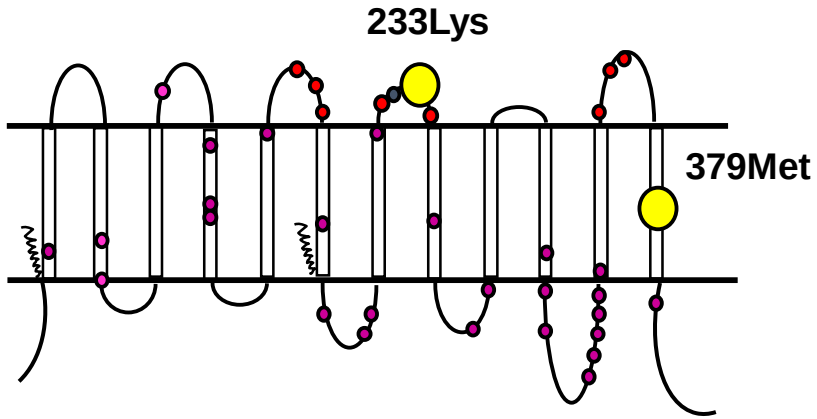
Other considerations

Despite serologic matching for Rh (D, C, E or D, C/c, E/e) antigens, patients remain at risk of forming alloantibodies to the Rh system due to the increased prevalence of *RH* variants in this patient population

Anti-Rh antibody formed despite Rh (D, C, E or D, C/c, E/e) matched transfusions → Comprehensive RH genotyping at a reference immunogenomics laboratory

Rh variants contribute to alloimmunization

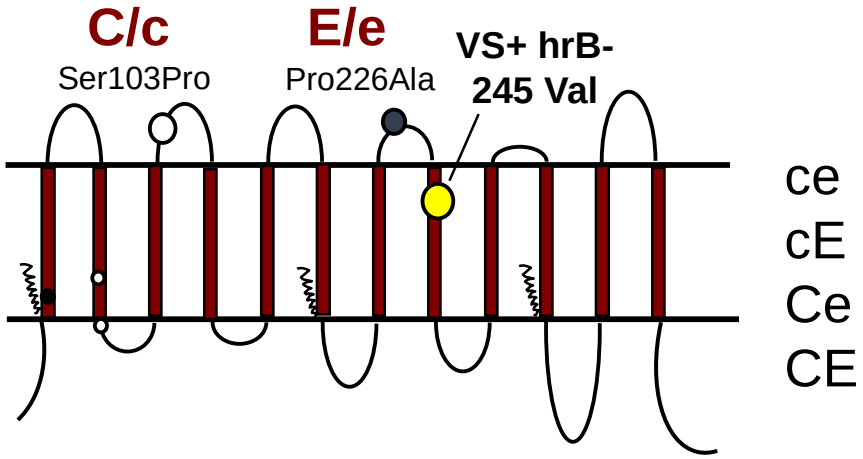
RhD



*RHD*DAU4*

Partial D+

RhCE



*RHCE*ce733G*

Partial e+, partial c+

- Variant alleles may encode partial antigens, cause loss of high prevalence antigens and/or generate novel antigens
- Serologic Rh typing detects the five principal antigens and do not reliably distinguish Rh variants

What to do when a delayed hemolytic transfusion reaction occurs

Defining DHTRs and/or hyperhemolysis

- DHTR is defined as a significant drop in hemoglobin within 21 days post-transfusion associated with one or more of the following:
  - new red cell alloantibody
  - hemoglobinuria
  - accelerated HbS% increase with a concomitant fall in HbA% post-transfusion
  - relative reticulocytopenia or reticulocytosis from baseline
  - significant LDH rise from baseline
  - exclusion of an alternative cause
- Hyperhemolysis is defined as a rapid hemoglobin decline to below the pretransfusion level and rapid decline of the post-transfusion HbA% level

Recommendation for management of DHTR

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

- Immunosuppressive therapy should be initiated promptly in patients with life-threatening hemolysis
- The potential harm of not providing immunosuppressive therapy to an individual experiencing a DHTR with ongoing hyperhemolysis is possible but unpredictable

Recommendation continued

- First-line: IVIg and high-dose steroids
- Second-line: eculizumab
- Rituximab is primarily indicated for potential prevention of additional alloantibody formation in patients who may require further transfusion
- When no antibody specificity is identified, avoidance of further transfusion is recommended unless patients are experiencing life-threatening anemia
  - If transfusion is warranted, consider extended matched red cells (C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, S/s)

How do we prevent a delayed hemolytic transfusion reaction in a high risk patient?

Rare clinical situations in which patients:

- are experiencing life-threatening anemia that require immediate red cell transfusion and compatible blood cannot be found (i.e., patients with alloantibodies for whom antigen-negative blood is unavailable)
- have a history of repeated episodes of severe hemolytic transfusion reactions with or without an antibody specificity identified (even when compatible blood is available)

Recommendation to prevent DHTRs in at risk patients

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

- Ongoing discussion is needed to weigh the potential benefits and harms associated with transfusion versus the impact of ongoing life-threatening anemia
- Consider the respective mechanisms of action for choice of therapy (IVIg, steroids, and/or rituximab)
- A shared decision-making process is critical

Considerations

- The morbidity and mortality associated with acute and delayed HTRs is weighed against the potential adverse effects typically experienced with immunosuppression
- Interventions aimed at inhibiting antibody-mediated hemolysis (i.e., IVIg and steroids) may be more effective in preventing a potential AHTR
- Efforts to prevent DHTR may benefit from immunosuppression that mitigates new alloantibody production (i.e., steroids, rituximab)

Approach to transfusions in chronic and acute settings

Recommendation for pre-operative transusion

The panel suggests preoperative transfusion over no preoperative transfusion in patients with SCD undergoing surgeries requiring general anesthesia and lasting >1 hour *(conditional recommendation, very low certainty in the evidence about effects)*

- Decision-making should be individualized based on:
  - genotype
  - the risk level of surgery
  - baseline total hemoglobin
  - complications with prior transfusions
  - disease severity
- Ideal to have total hemoglobin levels of >9 g/dl prior to surgery, and should provide RCE transfusion for patients who require preoperative transfusion but have a high hemoglobin level (>9-10 g/dl)

Rationale

- Surgical intervention results in:
  - increased mortality and morbidity in patients with SCD who undergo surgery
  - increased risk of postoperative pain crisis and ACS
- Treating with preoperative blood transfusion reduces the risks of postoperative complications
- Most beneficial in patients who are:
  - undergoing high-risk surgery (cardiac surgery or neurosurgery), patients with a low preoperative hemoglobin level (<9 g/dl), and patients with a more severe genotype (HbSS/HbSB^{o}thal) or phenotype
- Less beneficial in patients who are:
  - undergoing low-risk surgery, patients with a higher hemoglobin level (>10 g/dl) or HbF level, or those with a milder genotype (HbSC) or phenotype

Recommendation for chronic transfusion modality

The panel suggests using automated RCE over simple transfusion or manual RCE in patients with SCD (all genotypes) receiving chronic blood transfusions *(conditional recommendation, very low certainty in the evidence about effects)*

- Consideration should be given to the clinical indication, baseline and target total hemoglobin and HbS%, patient age, patient preferences (particularly if central venous access is needed), iron overload status and iron chelation compliance, feasibility, and availability of compatible red cells

Evidence*

- 14 comparative observational studies (total, 652 patients)
  - nine studies compared automated RCE to simple transfusion
  - six studies compared automated RCE to manual RCE
- compared to simple transfusion, automated RCE was associated with increased red cell unit requirement but was not associated with increased alloimmunization or adverse transfusion reactions
- automated RCE was associated with lower levels of iron overload
- automated RCE increased the odds of achieving the desired pre-procedure HbS with shorter procedure duration and increased intervals between procedures

** the certainty of evidence was judged to be very low, due to imprecision, inconsistency, and/or high risk of bias*

Considerations for mode of chronic transfusion therapy

Simple transfusion	Manual red cell exchange	Automated red cell exchange
Peripheral venous access	+/- indwelling central catheter	+/- indwelling central catheter
Fewest red cell exposures	Intermediate red cell exposures	Highest red cell exposures
Iron loading inevitable	Intermediate iron loading	Minimal iron loading
Potential circulatory overload	Minimizes blood volume shifts	Maintains isovolemia
Potential hyperviscosity	Requires trained personnel	Requires specialized device and personnel

Simple transfusion may be preferred over RCE for:

- Young patients with small total blood volume
- Highly alloimmunized patients (availability of red cell units)
- Patients who would require an indwelling catheter

Recommendations for acute chest syndrome

The panel suggests automated RCE or manual RCE over simple transfusions in patients with SCD and severe acute chest syndrome *(conditional recommendation, very low certainty in the evidence about effects)*

- RCE for rapidly progressive ACS, not responding to initial treatment with simple transfusion, or with high pre-transfusion hemoglobin level that precludes simple transfusion

The panel suggests either automated RCE, manual RCE or simple transfusions in patients with SCD and moderate acute chest syndrome *(conditional recommendation, very low certainty in the evidence about effects)*

- insufficient evidence to support automated RCE or manual RCE over simple transfusions in patients with SCD and moderate ACS

Rationale

- The guideline panel determined that there is very low certainty of evidence for a net health benefit or harm of RCE compared to simple transfusion to treat moderate or severe ACS
- Data limited with few publications, relatively few episodes of ACS that occurred mostly children, and a high likelihood of indication bias
- Although no evidence of benefit from RCE was identified, this does not imply that such an effect does not exist
- Automated RCE can reduce HbS levels more rapidly than manual RCE

Recommendation for pregnancy

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

- insufficient evidence to recommend a strategy of prophylactic transfusion rather than standard care
- consider prophylactic transfusion at regular intervals at the onset of pregnancy when:
  - history of severe SCD-related complications prior to current pregnancy to reduce recurrent pain episodes, acute chest syndrome or other (SCD-related) comorbidities
  - additional features of high-risk pregnancy

Rationale

- Pregnancy in SCD is associated with:
  - maternal and fetal morbidity and mortality
  - inflammatory and thrombogenic changes that promote vaso-occlusion
  - higher rate of SCD-related complications, including pain episodes, ACS, and death
  - increased risk of pregnancy-related complications, such as pre-eclampsia and miscarriage
  - increased rate of fetal complications, including low birth weight, small size for gestational age, and stillbirth
- Hydroxyurea is teratogenic in animal models at high doses

Evidence*

- 12 comparative observational studies and one randomized control trial (RCT) (total, 1312 patients)
- RCT of scheduled vs on-demand transfusions (n=72)*
  - Reduced odds of pain episodes in scheduled transfusion arm
  - No difference in fetal complications or neonatal death
  - Limitations: transfusions did not begin until end of second trimester for ~25% of participants, and 44% of on demand transfusion arm required transfusions for acute anemia
- Based on a lack of high-quality studies and limited data regarding the potential complications of transfusion in pregnancy, the guideline panel did not recommend prophylactic, scheduled transfusion over on-demand transfusion in pregnant women with SCD

**the certainty of evidence was judged to be very low, due to imprecision, inconsistency, and/or high risk of bias*

* Koshy et al, NEJM, 1988

Additional Topics in the Guidelines

- The guideline panel suggests *either* red cell exchange with isovolemic hemodilution or conventional RCE in patients with SCD receiving chronic transfusions (conditional recommendation)
- The guideline panel suggests iron overload screening by magnetic resonance imaging (MRI; R2, T2*, R2*) for liver iron content every 1 to 2 years compared to serial monitoring of ferritin levels alone in patients with SCD receiving chronic transfusion therapy (conditional recommendation)
- The guideline panel suggests against adding routine iron overload screening by T2* MRI for cardiac iron content compared with serial monitoring of ferritin levels alone in patients with SCD receiving chronic transfusion therapy (conditional recommendation)

Acknowledgments

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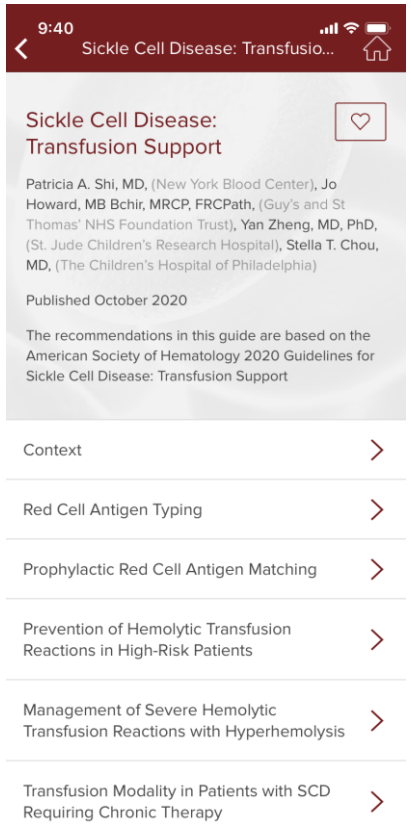
ASH Pocket Guides



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