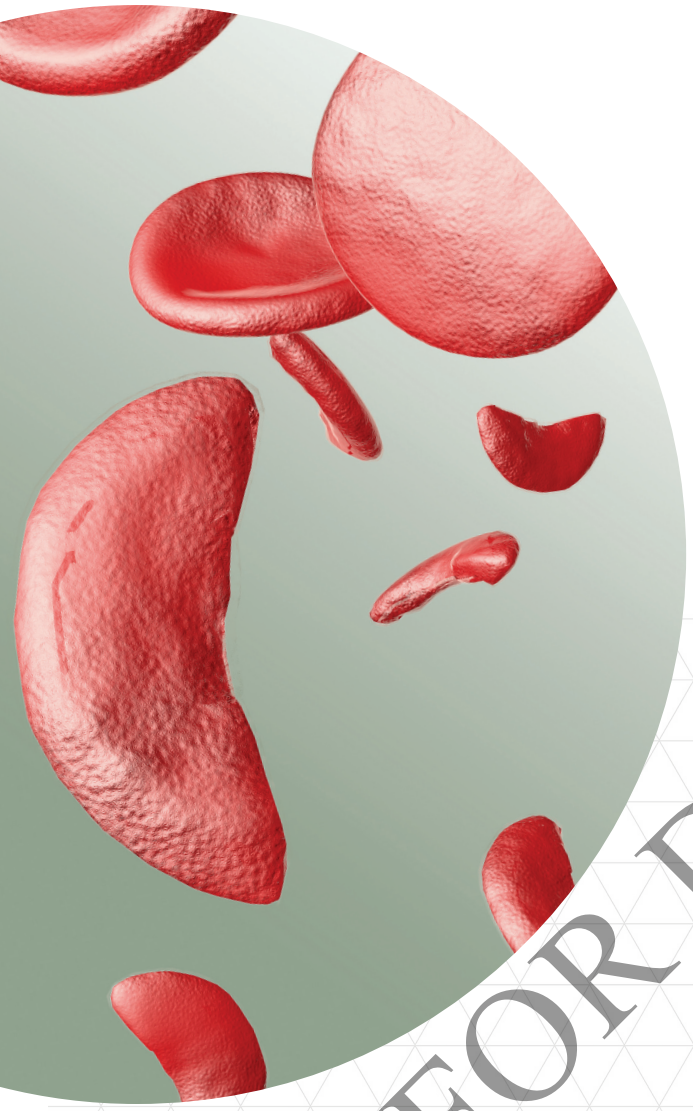
ASH CLINICAL PRACTICE GUIDELINES
SICKLE CELL DISEASE (SCD)

POCKET GUIDE



Sickle Cell Disease: Transfusion Support

A POCKET GUIDE FOR THE CLINICIAN

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Patricia A. Shi, MD, *New York Blood Center*
Jo Howard, MB Bchir, MRCP, FRCPath, *Guy's and St Thomas' NHS Foundation Trust*
Yan Zheng, MD, PhD, *St. Jude Children's Research Hospital*
Stella T. Chou, MD, *The Children's Hospital of Philadelphia*

The recommendations in this guide are based on the American Society of Hematology 2020 Guidelines for Sickle Cell Disease: Transfusion Support

Context

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. The information in this pocket guide is intended to support patients, clinicians, and other healthcare professionals in their decisions about transfusion support for SCD and the management of transfusion-related complications.

Red Cell Antigen Typing

The ASH guideline panel **suggests** an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before the first transfusion) C.

An extended red cell antigen phenotype will decrease time to antibody identification and time to transfusion. It should include C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s at a minimum. A serologic phenotype may be inaccurate if the patient has been transfused in the last 3 months. If feasible, genotyping is preferred, as it provides additional antigen information and provides increased accuracy for, among other things, C antigen determination and Fy^b antigen matching.

Prophylactic Red Cell Antigen Matching

The ASH guideline panel **recommends** prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions ✓.

Increasing the extent of matching reduces red cell alloimmunization incidence, thus reducing the risk of acute and delayed hemolytic transfusion reactions, difficulty finding antigen-compatible units, transfusion delays and hemolytic disease of the fetus and newborn.

Antibodies to Rh (D, C/c, E/e) and K are historically the most common specificities in patients with SCD, so all patients with SCD should receive blood that is matched for these antigens. Patients should also receive blood that is matched and antigen negative for any other clinically significant alloantibodies which are currently or have been historically detected. Extended red cell antigen matching (Jk^a/Jk^b, Fy^a/Fy^b, S/s) may provide further protection from alloimmunization, but identifying sufficient units may be difficult. Patients who have a GATA mutation in the *ACKR1* gene, which encodes Fy antigens, are **not at risk** for anti-Fy^b and may 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 encodes 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.

Table 1. Recommendations on Transfusion Management

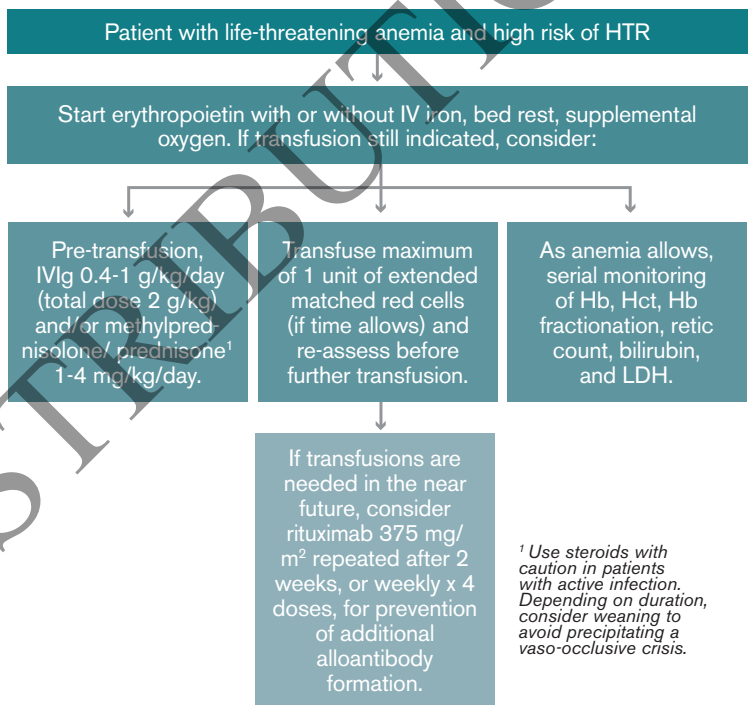
Initial visit (regardless of planned transfusion)	Obtain blood type, antibody screen, and extended red cell antigen profile (genotyping preferred)
Prior to transfusion	Obtain pre-transfusion antibody screen Match red cell units for: • Rh (D, C, E, or D, C/c, E/e) and K at minimum • Any other clinically significant alloantibodies previously detected
After transfusion	Patient should be counseled to return for symptoms of hemolytic transfusion reaction (increased jaundice, scleral icterus, fatigue, dark urine, pain) Ideally, obtain type and screen within 1-3 months to screen for new alloantibody formation
Best practice	Patients should carry a card with the primary institution's blood bank telephone number for other hospitals to obtain transfusion history, and stating she/he: • Requires Rh and K matched red cells • Requires additional antigen matching, if alloimmunized

Prevention of Hemolytic Transfusion Reactions in High-Risk Patients

The ASH guideline panel **suggests** immunosuppressive therapy (intravenous immunoglobulin [IVIg], steroids, and/or rituximab) over no immunosuppressive therapy in patients with SCD (all genotypes) with an acute need for transfusion and at high risk for acute hemolytic transfusion reaction or with a history of multiple or life-threatening delayed hemolytic transfusion reactions C.

This recommendation applies to patients who are not currently experiencing a hemolytic transfusion reaction (HTR), but have life-threatening anemia that requires immediate red cell transfusion, for which compatible blood cannot be found (i.e., patients with alloantibodies for whom antigen-negative blood is unavailable) and/or a history of repeated episodes of severe HTRs with or without an antibody specificity identified (even when compatible blood is available).

A shared decision-making process between the hematologist and transfusion medicine specialist is critical to consider choice of therapy based on respective modes of action of immunosuppressive agents. Efforts to prevent delayed HTR may include immunosuppression that mitigates new alloantibody production (i.e rituximab), whereas interventions aimed at inhibiting antibody-mediated hemolysis (i.e. IVIg and steroids) may be more effective in preventing a potential acute HTR.



Management of Severe Hemolytic Transfusion Reactions with Hyperhemolysis

The ASH guideline panel **suggests** immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) over no immunosuppressive therapy in patients with SCD (all genotypes) with a delayed hemolytic transfusion reaction and ongoing hyperhemolysis C.

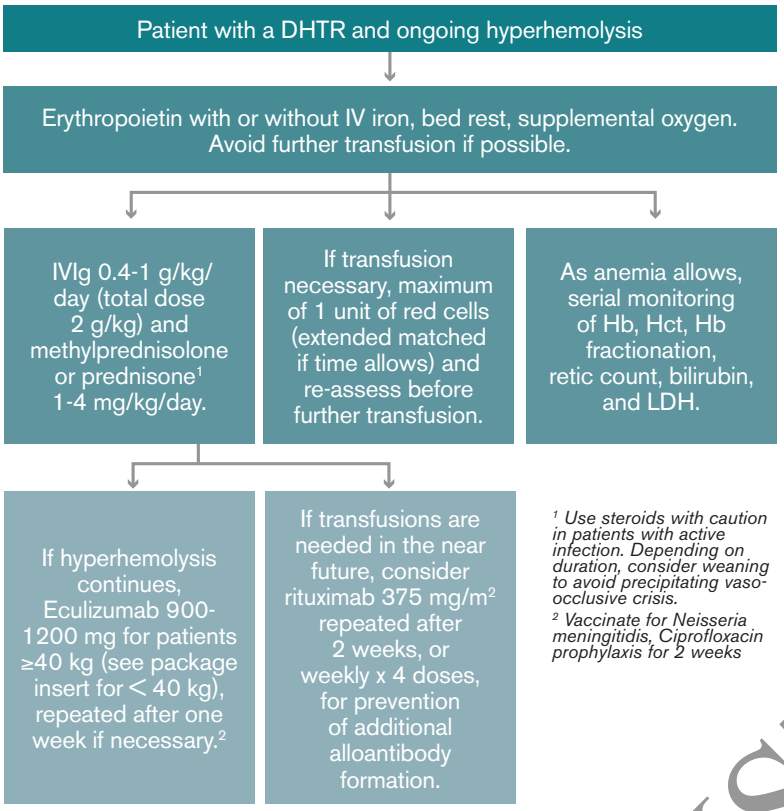
Immunosuppressive therapy should be initiated promptly in patients with severe HTR accompanied by hyperhemolysis. Hyperhemolysis can occur with no identifiable antibody and a negative direct antiglobulin test.

Table 2. Definitions of Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reaction (DHTR)	Significant drop in hemoglobin within 21 days posttransfusion associated with 1 or more of the following: • New red cell alloantibody • Hemoglobinuria • Accelerated increase in percentage hemoglobin S (HbS%) with a concomitant fall in HbA posttransfusion • Relative reticulocytopenia or reticulocytosis from baseline • Significant lactate dehydrogenase (LDH) rise from baseline • Exclusion of an alternative cause
Hyperhemolysis	• Rapid hemoglobin decline to below the pretransfusion level, and • Rapid decline of posttransfusion HbA level

Judicious use of further transfusion is critical. In patients without life-threatening anemia and with no antibody specificity identified, avoidance of further transfusion is recommended. A shared decision-making process between the hematologist and transfusion medicine specialist is critical.

Figure 2. Management of DHTR with Ongoing Hyperhemolysis



[1] Use steroids with caution in patients with active infection. Depending on duration, consider weaning to avoid precipitating vaso-occlusive crisis.

[2] Vaccinate for Neisseria meningitidis, Ciprofloxacin prophylaxis for 2 weeks

Transfusion Modality in Patients with SCD Requiring Chronic Therapy

The ASH guideline panel **suggests** using automated RCE over simple transfusion or manual RCE in patients with SCD (all genotypes) receiving chronic transfusions C.

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

With automated RCE, the target HbS%, hematocrit, and overall fluid balance is programmed. Patients with small total blood volumes may require priming (albumin or red cells) due to the extracorporeal volume of the apheresis machine. In the absence of iron chelation, neutral or negative iron balance is achieved by targeting an end Hct that is equal to or lower than the starting Hct.

Table 3. 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
Least red cell exposure	Intermediate red cell exposure	Most red cell exposure
Iron loading inevitable	Intermediate iron loading	Minimal iron loading possible
Potential circulatory overload	Minimizes blood volume shifts	Maintains isovolemia
Potential hyperviscosity to reach target HbS%	Long procedure time to reach target HbS%	Quickly and precisely reaches target HbS%
Standard nursing	Requires trained personnel	Requires specialized device and personnel

Transfusion for Patients with SCD and Acute Chest Syndrome

The ASH guideline panel **suggests** automated RCE or manual RCE over simple transfusions in patients with SCD and severe acute chest syndrome C.

The ASH guideline panel **suggests** automated RCE, manual RCE, or simple transfusions in patients with SCD and moderate acute chest syndrome C.

Acute chest syndrome (ACS) is one of the leading causes of death in patients with SCD and therefore prompt treatment is critical. In addition to transfusion therapy, interventions may include antibiotics, oxygen, invasive and noninvasive respiratory support, and bronchodilators. Severe ACS is typically accompanied by a rapidly falling hemoglobin concentration, severe hypoxia and/or a requirement of invasive respiratory support. Moderate ACS includes cases of ACS with no severe features. The decisions about whether to perform manual or automated exchange will depend on availability of apheresis devices, specialized staff and venous access.

Table 4. Choice of Transfusion Therapy in ACS

Consider simple transfusion:	Moderate ACS with pre-transfusion Hb level < 9 gm/dL
Consider automated or manual RCE: (automated preferred if available)	• Severe ACS • Rapidly progressive ACS • Moderate ACS with a high pre-transfusion Hb (e.g., ≥ 9 gm/dL) • No improvement after initial simple transfusion

Red Cell Exchange With or Without Isovolemic Hemodilution for Chronically Transfused Patients with SCD

The ASH guideline panel **suggests** either red cell exchange with isovolemic hemodilution (IHD-RCE) or conventional RCE in patients with SCD (all genotypes) receiving chronic transfusions C.

Isovolemic hemodilution – red cell exchange (IHD-RCE) is a procedure available on automated apheresis devices in which prior to RCE, the patient undergoes a red cell depletion with concurrent volume replacement (normal saline or 5% albumin). The potential benefit of IHD-RCE is a decrease in red cell unit exposure. There is no clear increased risk of harm when compared with conventional RCE, but given the paucity of data, IHD-RCE is not advised for acute indications (eg, stroke, acute chest syndrome) or when induction of further anemia during the IHD phase may be detrimental (eg, recent history of stroke or transient ischemic attack, severe vasculopathy or cardiopulmonary disease).

Table 5. Technical Considerations with IHD-RCE	
Minimum Hct	The guideline panel suggests not decreasing the Hct to <21% and/or no more than 20% from baseline.
Isovolemic replacement fluid	Saline or 5% albumin are standard. If hypotension is a concern, albumin should be considered.
To reduce red cell volume needed	Maintain same procedure frequency and targets for end Hct and HbS% as with conventional RCE.

Transfusion Management During Pregnancy

The ASH guideline panel **suggests** either prophylactic transfusion at regular intervals or standard care (transfusion when clinically indicated for a complication or hemoglobin lower than baseline) for pregnant patients with SCD (all genotypes) C.

Pregnancy in women with SCD is high-risk and associated with maternal and fetal morbidity and mortality. Pregnancy is associated with a higher rate of SCD-related complications including pain episodes, ACS, an increased risk for pregnancy-related complications to the mother and fetus as well as death. Because hydroxyurea may be teratogenic, the most commonly used treatment during pregnancy is red cell transfusion. Compared with on-demand therapy, chronic transfusion may positively affect maternal and neonatal outcomes, such as reducing maternal mortality, vaso-occlusive pain episodes, and pulmonary complications, as well as neonatal death and prematurity. In view of the risks associated with transfusion and the lack of definitive evidence, decisions about prophylactic transfusion should be individualized and made after discussions between the patient, hematologist and obstetrician.

Table 6. Transfusion Considerations during Pregnancy.	
Consider prophylactic regular transfusion at pregnancy onset for:	• History of severe or frequent SCD-related complications before current pregnancy • Additional features of high-risk pregnancy (e.g. co-morbidities such as nephropathy)
Consider prophylactic regular transfusion later in pregnancy for:	• Onset of SCD-related complications (fetal or maternal) during current pregnancy
Transfusion targets	• Hb >7 gm/dL and target HbS level (or S+C) of < 50%[1]
Alloimmunization risk	• Hemolytic disease of the fetus and newborn is a potential risk with transfusion

[1] *Based on expert consensus and experience*

Preoperative Transfusion for Patients with SCD

The ASH guideline panel **suggests** preoperative transfusion over no preoperative transfusion in patients with SCD undergoing surgeries requiring general anesthesia and lasting more than 1 hour C.

Surgery with general anesthesia is associated with increased mortality and morbidity in patients with SCD, particularly because of an increased risk for postoperative pain crisis and ACS. Decision-making should be individualized based on genotype, the risk level of surgery, baseline total hemoglobin, complications with prior transfusions such as DHTR, and disease severity.

Clinicians should aim for total hemoglobin levels of 9-10 gm/dL before surgery and should provide RCE transfusion for patients who require pre-operative transfusion but have a high hemoglobin level (>9-10 gm/dL) that precludes administration of simple transfusion.

Table 7. Pre-operative Transfusion Considerations	
Consider no transfusion:	• Surgery requiring less than one hour of general anesthesia • Low-risk surgery (ie. myringotomy tubes, arthroscopy) • Hb level > 10 gm/dL • Milder genotype (HbSC) or phenotype • Multiple red cell alloantibodies or history of severe DHTR
Consider simple transfusion:	• Moderate or high-risk surgery (i.e. abdominal surgery, tonsillectomy, joint replacement surgery) • Hb < 9 gm/dL • Severe genotype (HbSS/HbSB^{0}thal) or phenotype
Consider red cell exchange:	• Very high-risk surgery (e.g., neurosurgery or cardiac surgery) • Patients needing preoperative transfusion but with Hb > 9-10 gm/dL
Transfusion targets	• Post-transfusion target Hb 9-11 gm/dL • Pre-operative HbS% < 30-50% for high-risk surgery or a severe phenotype (e.g., history of stroke, recurrent ACS, or prior severe post-operative complications).

Screening for Transfusional Iron Overload

The ASH guideline panel **suggests** iron overload screening by magnetic resonance imaging (MRI; R_2, T_2*, or R_2*) for liver iron content every 1 to 2 years compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy C.

The ASH guideline panel **suggests *against*** adding routine iron overload screening by T_2* MRI for cardiac iron content compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy C.

Liver iron concentration by R_2 or R_2* MRI correlates better than serum ferritin with iron levels by liver biopsy. Cardiac iron loading generally occurs only with prolonged elevated liver iron content in patients with SCD. The serum ferritin level test is useful to monitor trends in iron burden over time. A major limitation in SCD is that inflammation can raise ferritin levels irrespective of iron burden.

Table 8. Iron Overload Screening with Chronic Transfusion	
Consider serum ferritin monitoring only:	• Serum ferritin < 1000 ng/mL, particularly if managed with regular exchange transfusion with neutral or negative net red cell gain
R2, T2*, or R2* MRI	• Use a validated method[1] • The same method should be used over time (every 1-2 years if indicated) • Useful for titration of iron chelation (and to determine when to discontinue chelation), regardless of ferritin level
Consider cardiac MRI:	• Liver iron content > 15 mg/g dry weight for ≥ 2 years • History of exceptionally elevated liver iron • Evidence of end organ damage resulting from transfusional iron overload • Evidence of cardiac dysfunction
Consider chelation:	• R_2 or R_2* liver iron concentration > 5 mg/g dry weight • T_2* cardiac iron < 20 ms

[1] *Refer to a specialized center if not available at your institution.*

Strength of Recommendations and Quality of Evidence

The methodology for determining the strength of each recommendation and the quality of the evidence supporting the recommendations was adapted from GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926. More details on this specific adaptation of the GRADE process can be found in American Society of Hematology 2019 Guidelines for Sickle Cell Disease: Transfusion Support.[1]

Strength of Recommendation	
✓	**Strong recommendations** - 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.
C	**Conditional recommendations** - Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

How to Use This Pocket Guide

ASH pocket guides are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. The information included in this guide is not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the unique clinical presentation of an individual patient, ideally through a shared process that considers the patient's values and preferences with respect to all options and their possible outcomes. Decisions may be constrained by realities of a specific clinical setting, including but not limited to institutional policies, time limitations, or unavailability of treatments. ASH pocket guides may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, these pocket guides may become obsolete. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

The complete 2020 ASH Clinical Practice Guideline for Sickle Cell Disease: Transfusion Support[1] include additional remarks and contextual information that may affect clinical decision making. To learn more about these guidelines, visit ***hematology.org/SCDguidelines***.

Conflict of interest information for Drs. Liem, Lanzkron, Osunkwo, and Verhovsek may be found at ***hematology.org/pocketguidesCOI***.

[1] *Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2019 guidelines for sickle cell disease: Transfusion Support.* Blood Adv. *2020;4(2):327-355.*

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American Society of Hematology
2021 L Street NW, Suite 900
Washington, DC 20036
www.hematology.org

For expert consultation on transfusion in sickle cell disease and other hematologic questions, submit a request to the ASH Consult a Colleague program at ***www.hematology.org/Consult*** (ASH members only).