Transfusion Support

An Educational Slide Set

American Society of Hematology 2020 Guidelines for Sickle Cell Disease

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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.

ASH Clinical Practice Guidelines on SCD

1. Cardiopulmonary and Kidney Disease
2. **Transfusion Support**
3. Cerebrovascular Disease
4. Acute and Chronic Pain
5. Stem Cell Transplantation

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.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How to use these recommendations

	STRONG Recommendation ("The panel recommends…")	**CONDITIONAL Recommendation** ("The panel suggests…")
For patients	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.

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

Objectives

By the end of this session, you should be able to:

1. Describe recommendations on the prevention and management of alloimmunization
2. Describe recommendations on the prevention and treatment of hemolytic transfusion reactions
3. Describe recommendations for managing transfusion therapy for patients who require chronic transfusion support, for treatment of acute chest syndrome, for pregnant patients, and for patients undergoing surgeries requiring general anesthesia

BACKGROUND

"Most patients with SCD will have received a blood transfusion by the time they reach adulthood."

Background

- Practice varies on when an extended red cell antigen profile is obtained, the extent of antigen typing, and whether serologic or molecular methods are used
- Acute and delayed hemolytic transfusion reactions (HTRs) are among the most challenging complications of transfusion support in patients with SCD
- Practice varies in the use and method of transfusion for treatment or prevention of complications related to SCD

CASE 1

Red Cell Antigen Profiling and Prophylactic Antigen Matching

Case 1: Red cell antigen profiling

A three year old male with HbSS, presents to your clinic for an annual visit. A recent transcranial doppler shows elevated velocities in the right middle cerebral artery. You recommend that he begin a chronic transfusion program. He has not been previously transfused and you note that he has not had a red cell antigen profile.

What red blood cell antigen profiling should you obtain prior to transfusing the patient?

a. ABO, D only by serology
b. at least ABO, D, C/c, E/e, K, by serology
c. at least ABO, D, C/c, E/e, K, by genotyping
d. at least ABO, D, C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, S/s by serology or genotyping

Recommendation

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)*

- An extended red cell antigen profile includes C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s at a minimum
- Red cell antigen profiles should be made available across hospital systems
- A serologic phenotype may be inaccurate if 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

Case 1 continued: Prophylactic red cell matching for transfusion

You have obtained an extended red blood cell antigen profile by genotyping prior to this child's first transfusion. He is scheduled for transfusion tomorrow. When ordering his blood, the blood bank would like to know which red cell antigens to match?

C	-	Fy^a	-
c	+	Fy^b	- *
E	-	M	+
e	+	N	+
K	-	S	-
Jk^a	+	s	+
Jk^b	-		

* has the GATA mutation which results in loss of Fy^b expression on red cells only, so patient is not at risk for anti- Fy^b

Which antigens should this patient be matched* for (choose all that apply)?

a. ABO, RhD

b. ABO, RhD, Rh (C, E or C/c, E/e)

c. ABO, RhD, Rh (C, E or C/c, E/e), K

d. ABO, RhD, Rh (C, E or C/c, E/e), K, Jk^a, Jk^b, Fy^a, Fy^b, S, s

*provide antigen negative units if antigen negative, but may provide antigen negative or positive units if antigen positive

Recommendation

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)*

- The extended red cell antigen profile may be determined by genotype or serology
- Extended red cell antigen matching (Jk^a/Jk^b, Fy^a/Fy^b, S/s) may provide further protection from alloimmunization, 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
- Alloantibodies can make it difficult, and at times, impossible to find compatible units
- Alloantibodies may cause hemolytic transfusion reactions
- Prevention of antibody formation may avoid hemolytic transfusion reactions, difficulty in identifying sufficient antigen-negative units and transfusion delays

Evidence

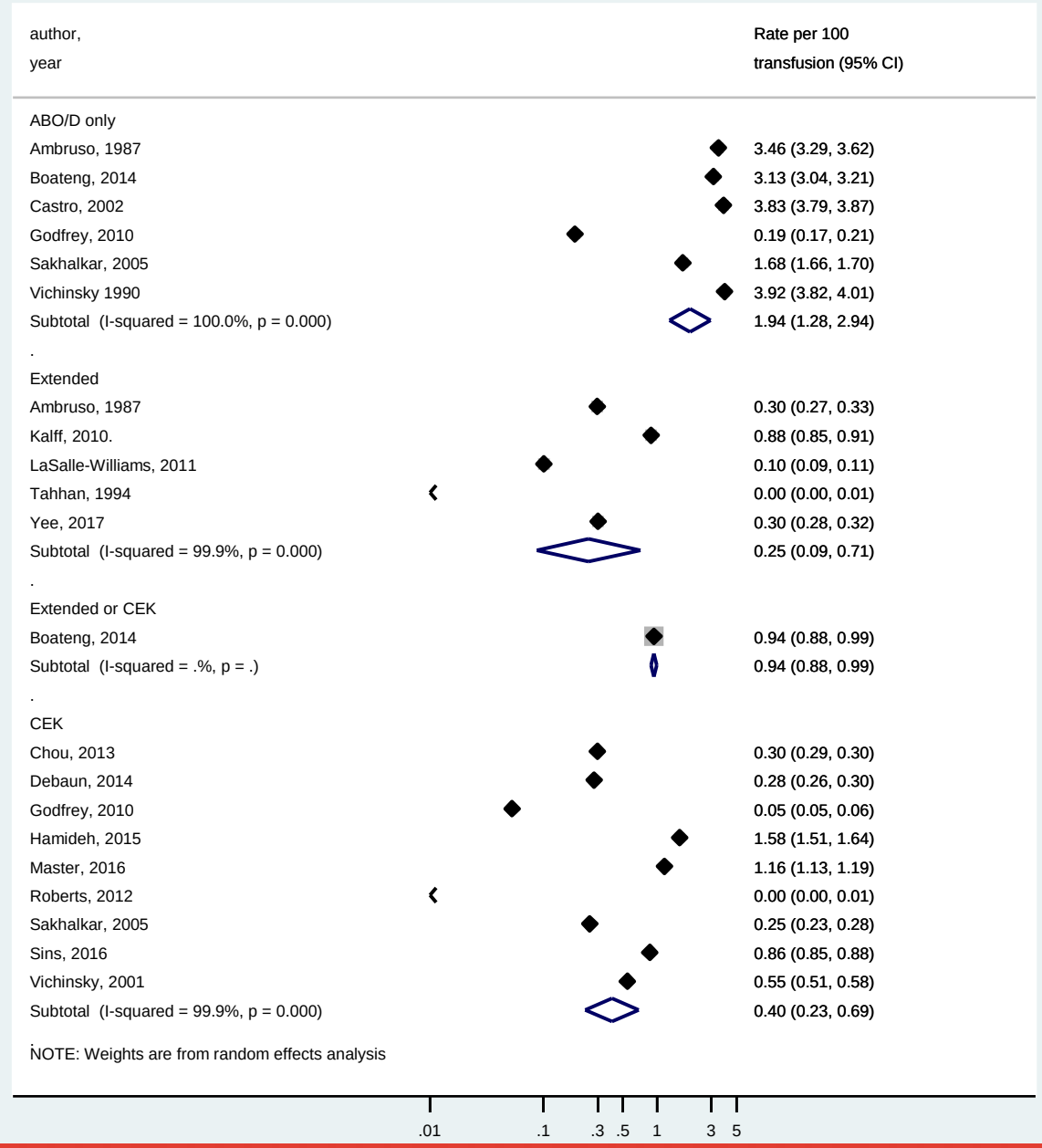
- The systematic review identified **28 studies (total, 2,535 patients).**
- Only 2 primary observational comparator studies directly compared the **alloimmunization incidence rate** in patients with SCD transfused with either phenotypically matched red cells (Rh, K-matched or extended matched) or ABO/RhD-matched red cells
  - 0.053 Abs/100 trxns (Rh- and K-matched) vs. 0.189 Abs/100 trxns (ABO/RhD-matched)*
  - 0.9 Abs/100 trxns (Extended matched) vs. 3.1 Abs/100 trxns (ABO/RhD-matched)**

* Godfrey GJ et al. *Pediatr Blood Cancer*. 2010
** Boateng L et al. *International Journal of Laboratory Hematology.* 2014

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



Summary for red cell antigen typing and matching

- Extended red cell antigen profiling is superior to ABO/RhD typing for all patients with SCD at the earliest opportunity (optimally prior to first transfusion)
  - If possible, red cell antigen genotyping is the preferred method
- Prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching is recommended for patients with SCD receiving transfusions (strong recommendation)
  - Extended matching to include Fy^a/Fy^b, Jk^a/Jk^b, S/s further reduces alloimmunization risk but may be challenging to identify sufficient 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

CASE 2

Hemolytic transfusion reactions

Case 2: management of severe DHTRs

A 34 year old patient with HbS-beta^0 thalassemia develops fever, dark urine, and flank pain a week after a transfusion for pre-operative preparation. His hemoglobin of 5.6 g/dL is 2 g/dL lower than his pre-transfusion hemoglobin. The antibody screen is positive but no antibody specificity is identified by the blood bank. What is the best first step in his management?

a. Steroids +/- IVIg
b. Eculizumab
c. Rituximab
d. Transfuse PRBCs

Recommendation

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)*

Recommendation continued

- 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 continued

- 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
- 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)

Case 2 continued: Preventing hemolytic transfusion reactions

This patient has now had three similar episodes. Going forward, the best course of action for this patient, who has a history of delayed hemolytic transfusion reactions, would be to manage with the following (choose all that apply):

a. No additional precautions
b. Delay transfusion
c. ABO, Rh, and extended matched red cell units
d. Steroids +/- IVIg
e. Rituximab >4 weeks prior to transfusion for pre-operative preparation

Recommendation

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

These are 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)

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)

Summary of management and prevention of HTRs

- Acute and delayed HTRs are among the most challenging complications of transfusion support in patients with SCD

- 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)*

Summary of management and prevention of HTRs

- 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)*

CASE 3

Approach to transfusions in chronic and acute settings

Case 3

An 8-year-old patient with HbSS had a sleep study showing sleep apnea and needs a tonsillectomy and adenoidectomy. The ENT surgeon has asked for pre-operative management recommendations with regards to a transfusion plan. His hemoglobin is 7 gm/dL. The procedure will take a little over one hour. The best response is:

a. no transfusion needed
b. red cell exchange (automated or manual)
c. simple transfusion
d. 1.5x maintenance intravenous hydration 12 hours prior to surgery

Recommendation

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

Case 3 continued

Your patient with HbSS is now 12 years old and presents to the ER with right sided hemiplegia. His MRI showed findings consistent with an ischemic stroke. He was exchanged transfused acutely and will require chronic red cell transfusions as an outpatient. Your center offers simple transfusion, manual red cell exchange and automated red cell exchange. Which program should this patient be initiated on (choose all that apply)?

a. simple transfusion
b. manual red cell exchange
c. automated red cell exchange

Recommendation

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

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

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*

Summary of mode of chronic transfusion therapy

- Compared to simple transfusion, the primary potential benefit of RCE is the reduced iron overload
- Compared to manual RCE, the main benefits of automated RCE are improved HbS suppression, reduced procedure time, and reduced procedure frequency with no significant evidence of increased risks
- 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

Case 3 continued

Your 12-year-old patient has missed several transfusion appointments for secondary stroke prophylaxis. He now presents to the emergency room with fever and cough. His chest X-ray shows a right middle lobe infiltrate and oxygen saturation is 89% and his work of breathing is rapidly escalating. You have decided to to transfuse him; which is the optimal approach?

a. simple transfusion
b. manual RCE
c. automated RCE

Recommendation

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

Case 4

A 25 year old woman with HbSS notifies you that she had a positive pregnancy test. The pregnancy is confirmed to be at about 8 weeks gestation. She typically has several admissions per year for vaso-occlusive episodes. She asks you about your plan for prenatal care as it pertains to transfusions. The best responses are (choose all that apply):

a. scheduled transfusions at regular intervals
b. transfusions only for acute issues (complications or lower than baseline hemoglobin)
c. no transfusions during pregnancy
d. medical management with fluids and hydroxyurea

Recommendation

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

Summary for transfusion in ACS, pre-operatively, and pregnancy

- Automated RCE or manual RCE is suggested over simple transfusions in patients with SCD and **severe** acute chest syndrome *(conditional recommendation)*
- Either automated RCE, manual RCE or simple transfusions is suggested in patients with SCD and **moderate** acute chest syndrome *(conditional recommendation)*
- Preoperative transfusion is suggested over no preoperative transfusion in patients with SCD undergoing surgeries requiring general anesthesia and lasting >1 hour *(conditional recommendation)*
- **Either** prophylactic transfusion at regular intervals or standard care (transfusion when clinically indicated for a complication or hemoglobin lower than baseline) is suggested for pregnant patients with SCD *(conditional recommendation)*

Additional Topics in the Guidelines

- Red cell exchange with or without isovolemic hemodilution for chronically transfused patients with SCD
- Screening for transfusional iron overload

Future Priorities for Research

- Comparison of serologic vs genotypic matching, notably for Rh system
- Outcomes from immunomodulation used to treat or prevent hemolytic transfusion reactions
- Role of red cell transfusion in pregnancy
- Optimal management of pre-operative transfusion
- Comparison of outcomes between simple vs exchange transfusion for patients requiring chronic red cell therapy or for treatment of acute complications
- Data regarding clinical significance of varying degrees of iron overload

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- See more about the ASH SCD guidelines: https://hematology.org/scdguidelines