2. Transfusion

Principles

- There are specific indications for the use of red cell transfusions for individuals with sickle cell disease.
- Two main indications for red cell transfusion are to treat severe exacerbations of anemia and to treat and/or reduce the complications of sickle cell disease.
- Patients with sickle cell disease should be transfused with phenotypically matched red cells to reduce the risk of alloimmunization and hemolytic transfusion reactions.
- After receiving red cell transfusions, patients should be closely monitored for acute and delayed transfusion reactions.

Background

Individuals with sickle cell disease (SCD) have elevated blood viscosity, which may be further exacerbated by increases in hematocrit. In addition, they are more likely to experience delayed hemolytic transfusion reactions. For these reasons, the indications for transfusion in patients with SCD differ significantly from those in other patients. They are as follows:

1. **Exacerbation of anemia:** In the absence of heart failure, dyspnea, hypotension, or marked fatigue, transfusion should be avoided unless the hemoglobin (Hb) has decreased to <50 to 60 g/L.[1] Note that due to the short circulating life span of sickle erythrocytes, a rapid decrease in Hb can occur if the reticulocyte count falls below a patient's baseline.
2. **Treatment or prevention of SCD complications:** In patients receiving transfusion, hemoglobin concentration should not be increased above 100 to 110 g/L.[2] Note that augmentation of oxygen delivery in patients with SCD is achieved more efficiently through decreasing the sickle hemoglobin percentage (HbS%) than by increasing the total hemoglobin level, particularly at low shear blood flow.[3]

Recommendations

A1. Special Transfusion Requirements

The following apply to patients with sickle cell disease. No special precautions are required for patients with sickle cell trait (HBAS).

- Notify the hospital's Blood Transfusion Service when a patient with SCD presents to the emergency department or is admitted to hospital and transfusion is anticipated. This will allow for sufficient time to prepare specialized blood products. If possible, also provide blood bank with details of prior transfusions, including hospital location.

A2. Phenotypically Matched Red Blood Cells (RBCs)

- Determine the extended RBC phenotype (Rh, Kell, Duffy, Kidd and MNS blood groups) at first visit. Note that by using hypotonic (0.3%) saline lysis, blood samples from even recently transfused sickle cell patients may be phenotyped. Consider referring patients with SCD for genotyping studies, if available, due to the high prevalence of variant RBC antigen alleles. The *RHD-CE(3-7)- D* hybrid gene, for example, found in 22% of individuals of African descent, encodes a partial C antigen which will test as positive by traditional phenotyping, but which may allow the elaboration of an anti-C antibody in response to the transfusion of C+ RBCs if not balanced by a normal C antigen in the patient's other haplotype.[4]
- In patients with no previous alloantibodies, selecting RBCs matched for the patient's Rh (C, c, E, e) and Kell (K1) antigens is considered the most effective means of preventing sensitization, which may occur in up to 30% of sickle cell patients receiving blood matched only for ABO and Rh with D antigen.[5] A high proportion of alloantibodies in sickle cell patients will become undetectable on later testing;[6] if inadvertently challenged with an incompatible unit (e.g., at a health-care facility unaware of a patient's previous antibody history), a delayed hemolytic transfusion reaction may occur, which may trigger a vaso-occlusive pain episode and, in rare cases, may be complicated by hyperhemolysis (see next page).

- Individuals who have previously made alloantibodies may represent "high responders" who are at higher risk of making further antibodies with transfusion.[7] It is therefore prudent to extend prophylactic matching in such individuals by selecting RBCs that are matched for the patient's Rh (antigen D, C, c, E, e), Kell (K1), Kidd (Jk^a, Jk^b), Duffy (Fy^a) and S (S,s) antigens, as well as any antigens to which the patient has already made a clinically significant antibody.[8] Matching for Fyb in sickle cell patients is generally not necessary due to strong association in this population between the FYB gene and a GATA promoter mutation, which blocks only erythroid expression of the antigen; the continued expression of Fy^b in non-erythroid tissues prevents sensitization to this antigen.[9]
- Contacting other hospitals where a patient with SCD may have been transfused is advisable, as there may be a history of antibodies not currently reacting in their pre-transfusion group-and-screen effort; in some regions of Canada, Canadian Blood Services maintains a central registry of patients with SCD to facilitate the sharing of information. In Quebec, all bloods banks use the same information system, and transfusion history is readily available.
  NOTE: Life-saving transfusion should not be deferred if prophylactically phenotype-matched RBCs are not immediately available.

A3. Sickledex®-negative Blood

- RBC units that test positive by Sickledex® test (or dithionite solubility test) are from donors with sickle cell trait (HbAS). Since this blood will confound post-transfusion measurements of the patient's HbS%, it should be avoided if possible.[10]

B. Exchange Transfusion

- Ensure patient is euvolemic before initiating an exchange transfusion.
- Depending upon a patient's initial Hb, it may not be possible to achieve a specific target HbS% by simple transfusion without exceeding a total Hb of 100 to 110 g/L. Exchange transfusion may therefore be required to reach the traditional HbS% goal of <30%. (Note that, for HbSC, it is preferable to state goal as HbA% >70%.)

B1. Manual/Partial-exchange Transfusion:

- A typical protocol for adult manual/partial-exchange transfusion: (Note that, for children, smaller comparable volumes – e.g., 10 mL/kg – would be used.)
  1. Phlebotomize 1st 500 mL of whole blood. Note: For patients who are very anemic at baseline (e.g., Hb <70 g/L), a simple transfusion may be required before first phlebotomy.
  2. Administer a bolus 500 mL of 0.9% normal saline.
  3. Phlebotomize 2nd 500 mL of whole blood.
  4. Transfuse 2 units of RBCs. (Note that, for children, the total amount of red cells that are infused should correlate to the amount of whole blood that is removed. For small children with Hb near 100 g/L, for every 10 mL/kg whole blood phlebotomized, transfuse 5 mL/kg packed red cells.)
  5. Repeat as necessary to achieve target HbS% (typically a 1.5 blood volume exchange is necessary for first treatment; single cycles may be adequate for maintenance therapy). For patients starting with Hb near 100 g/L, step 4 should alternate between transfusion of 1 and 2 units to keep total Hb from exceeding 120 g/L.

B2. Automated Exchange/Erythrocytapheresis

- Automated exchanges are faster and more precise than manual exchanges, but require specialized equipment and trained personnel. Below is a typical procedure for automated exchange/erythrocytapheresis:
  1. Patient height, weight, and hematologic indices are programmed into an apheresis device.

2. Small aliquots of whole blood are withdrawn under pressure, RBCs separated by centrifugation and discarded, plasma and platelets returned to patient accompanied by donor RBCs (usually through separate line). Depending on the hospital protocol, donor RBCs may or may not be centrifuged in advance to reduce the quantity of optimal additive solution (e.g., SAG-M) infused.
3. Cycle repeats until goal Hb and HbS% achieved.

B3. Venous Access

- A central venous-access device placement is often required for exchange transfusions. If it is left in place between treatments, anticoagulation may be considered due to the risk of line-associated thrombosis.[11]
- Rigid tubing (e.g., dialysis line) or specialized subcutaneous access devices (e.g., Vortex® port) is required for most apheresis devices if the procedure cannot be performed using peripheral veins.

C. First-line Indications for RBC Transfusion

C1. Therapeutic Indications

1. Aplastic Crisis

- Most commonly due to parvovirus B19 infection
- Manifests as profound reticulocytopenia following a viral illness; resolves after 1 week with induction of neutralizing antibodies; 75% of patients develop immunity by age 20.[12]
- Due to decreased lifespan of sickle RBCs (16-20 days), a significant fall in Hb will occur before the reticulocyte count recovers.[13]
- Transfusion support may be required if anemia is symptomatic or if Hb <50 g/L. As there is usually a compensatory increase in plasma volume, however, transfuse cautiously to avoid volume overload (e.g., consider a pre-transfusion diuretic).
- In patients with impaired humoral immunity, intravenous immunoglobulin (IVIG) 0.5 g/kg weekly x 4 may speed viral clearance, but this is usually not required in SCD.[14]

2. Splenic Sequestration Crisis (*for more details on diagnosis and management of Splenic Sequestration, see Part II, section 8*)

- Trapping of sickle erythrocytes in sinusoids results in massive, painful enlargement of the spleen and severe anemia over a period of hours, which is accompanied by reticulocytosis and, occasionally, thrombocytopenia and leukopenia.
- If untreated, sequestration crises cause death from hypovolemic shock/anemia; immediate transfusion is often required. Post-transfusion Hb levels are often higher than expected, however, suggesting autotransfusion as sequestered RBCs are released back into circulation. To avoid accidental polycythemia and hyperviscosity, transfuse 1 unit at a time, reassessing Hb level before administering additional red cells. In children, consider administering RBCs in smaller than normal aliquots (e.g., 3 to 5 mL/kg). A single transfusion is often sufficient to reverse a sequestration crisis.[15]
- Following stabilization, secondary prevention strategies must be actively considered on a patient-by-patient basis (*see Part II, section 8 on Splenic Sequestration*).

3. Hepatic Sequestration Crisis

- Less commonly, patients may present with hepatic sequestration crises, characterized by a rapidly enlarging liver accompanied by a decrease in hemoglobin, a rise in reticulocyte count, and a conjugated hyperbilirubinemia. Alkaline phosphatase and transanimases may also be variably increased.
- As with splenic sequestration crises, transfusions should also be administered cautiously due to the risk of autotransfusion and hyperviscosity. Recurrences are common.[1]

4. Acute Chest Syndrome (*see Part II, section 2 on Acute Chest Syndrome*)

- Broadly defined as a new infiltrate on chest x-ray in a patient with SCD, associated with one or more symptoms of fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia; may progress rapidly to respiratory failure and be complicated by neurologic events.[17]
- May be triggered by infection (often atypical organisms) or marrow embolism as complication of vaso-occlusive pain episode; specific cause not identified in ~60% of cases despite extensive investigations.[17] Empiric treatment with bronchodilators, incentive spirometry and antibiotics (e.g. macrolide or quinolone) advisable in all patients.
- RBC transfusion in the setting of acute chest syndrome results in improved oxygenation.[17] Some studies have observed equivalent outcomes whether patients are treated with exchange transfusion (HbS% goal of 30%) or simple transfusion (Hb goal of 100 g/L).[18] Other studies have found, however, that patients receiving top-up transfusions may progress to requiring a full exchange.[19]
- In the absence of evidence from randomized controlled trials, most patients with acute chest syndrome should be transfused, with exchange transfusions reserved for patients with more severe or rapidly progressing disease.[20] Signs of severe disease include:
  - altered mental status
  - persistent heart rate >125 beats/minute, respiratory rate >30 breaths/minute, temperature >40°C, or worsening hypotension
  - arterial pH <7.35; peripheral capillary oxygen saturation (SpO2)% <88% despite aggressive ventilatory support
  - serial decline in SpO2% or alveolar-arterial gradient
  - fall in hemoglobin >20 g/L
  - platelet count <200/fL
  - elevated troponin or brain natriuretic peptide (BNP)
  - evidence of multiorgan failure (e.g., renal or hepatic dysfunction)
  - pleural effusions or progressive pulmonary infiltrates

5. Progressive Cholestasis

- This is a syndrome that may occur in the absence of cirrhosis, marked by right upper quadrant pain, nausea, extreme elevation of bilirubin (predominantly conjugated) and alkaline phosphatase and variable elevation in transanimases. It is accompanied by renal failure, thrombocytopenia, and prolonged coagulation times. This syndrome occurs secondary to sickling within hepatic sinusoids, resulting in intrahepatic cholestasis.[21]
- All survivors have been treated with RBC exchange transfusion; platelet and plasma transfusion support have been used to control bleeding due to hemostatic failure.[1]
- In contrast, benign cholestasis (unaccompanied by fever, abdominal pain, gastrointestinal symptoms, or hepatic synthetic failure) resolves within months without specific therapy.[1]

6. Acute Ischemic Stroke or Retinal Occlusion (*see Part II, section 4 on Stroke and Neurological Complications*)

- RBC transfusion is recommended for all pediatric patients. Within 3 hours of the first unit of transfused RBCs, middle cerebral artery (MCA) flow velocity decreases by 20%.[22] Exchange transfusion is associated with lower stroke recurrence rate than simple transfusion.[23]
- Although there is less supportive evidence for it, RBC transfusion is recommended for adult sickle cell patients without other obvious stroke etiology (e.g., cardioembolism).[15] Note, however, that most strokes in young adult patients with SCD are hemorrhagic, a condition for which the benefits and safety of immediate transfusion therapy are unclear.[24]

C2. Prophylactic Indications

1. Perioperative (*see Part III, section 1 on Peri-Operative Management*)

- The value of pre-operative transfusion in the prevention of post-operative sickle cell complications was established in the 2013 TAPS trial, in which patients with HbSS or HbS beta^0-thalassemia were randomized to pre-operative transfusion vs no transfusion. The transfusion protocol itself required transfusing to a hemoglobin of 100 g/L within 10 days of surgery, with patients starting with a hemoglobin of >90 g/L undergoing a partial exchange transfusion with a target HbS <60%. The trial was stopped early due to a strong treatment effect: the rate of clinically important complications decreased from 39% in the untransfused group to 15% in the transfused group, and 91% of serious adverse events were acute chest syndromes.[26]
- The 2013 TAPS trial, however, did not enroll patients undergoing high-risk surgeries (e.g., cardiovascular or neurosurgical procedures), and excluded high-risk patients (e.g., patients with previous acute chest syndrome requiring intubation or baseline oxygen saturation <90%). High-risk procedures and high-risk patients were similarly excluded from an earlier randomized controlled trial of patients with HbSS that demonstrated no benefit of an aggressive pre-operative transfusion strategy (target HbS <30%) over a more conservative strategy of simple transfusion to hemoglobin of 100 g/L (effectively achieving a HbS of 60%).[25] It is therefore unknown whether high-risk patients or those undergoing high-risk procedures might benefit from a more aggressive transfusion strategy than was provided in the TAPS trial.
- There is little evidence to guide transfusion practice in high-risk patients undergoing high-risk procedures. There is also, however, little evidence to guide transfusion practice in low-risk patients undergoing low-risk procedures. While low-risk procedures were included in the TAPS study, relatively few low-risk patients undergoing low-risk procedures were enrolled (13/70) due to the premature conclusion of the trial. Moreover, of the 11 serious adverse events recorded, only 1 was in a patient undergoing a low-risk procedure.[26] It is unknown whether low-risk patients undergoing low-risk procedures require pre-operative transfusion.
- There have been no randomized controlled trials demonstrating the benefit of pre-operative transfusion in patients with milder forms of SCD such as HbSC. Observational studies, however, suggest a benefit of pre-operative transfusion for these patients as well, if undergoing moderate to high-risk procedure.

2. High Stroke Risk (*see Part II, section 4 on Stroke and Neurological Complications*)

- In children, transfusion indicated for secondary prevention of ischemic stroke and for primary prevention in patients with high-risk features (e.g., high MCA or internal carotid blood flow by pediatric transcranial ultrasound, silent cerebral infarct). In the latter group, maintaining HbS <30% while keeping total Hb <120 g/L results in a 92% reduction in stroke incidence.[27]
- Once initiated, transfusions should be continued indefinitely, as discontinuation is associated with a high risk of stroke recurrence.[27] Transfusion has also been shown to be more effective than hydroxyurea in secondary stroke prevention.[28] Even with chronic suppression of HbS to less than 30%, regular monitoring by cerebral magnetic resonance imaging/angiography is advised, as a significant proportion of patients may still demonstrate radiologic disease progression, which in turn predicts overt neurologic symptom development.[29]
- There is little evidence to guide initiation of transfusions for stroke prophylaxis in adults, or following primary hemorrhagic strokes. Note that most strokes in young patients with SCD are hemorrhagic, and may occur despite normal transcranial Doppler screening.[24] However, the underlying pathophysiology for both thrombotic and hemorrhagic strokes in SCD is likely the same and therefore should both be managed with transfusions for secondary prophylaxis.[30]

D. Second-line Indications for RBC Transfusion

- In the absence of evidence from clinical trials, the initial therapeutic goal for the following indications should be HbS% <30%, with scheduled regular review of the transfusion regimen, and re-assessment if the patient's condition changes. Adjustments in transfusion goals and regimen (e.g. exchange versus simple transfusion) should be based on clinical factors.
- Note that some of the following conditions (priapism, pulmonary hypertension, malleolar ulcers) may represent complications of chronic intravascular hemolysis (e.g., nitric oxide depletion) rather than acute vaso-occlusion.[31]

D1. Recurrent Pain Episodes/Acute Chest Syndrome (see Part II, Section 2 on Acute Chest Syndrome)

- In patients who have failed an adequate trial of hydroxyurea (e.g., no benefit despite maximal tolerated dose), chronic transfusion support may be considered as a means of *preventing* recurrent vaso-occlsuive pain episodes or acute chest syndrome. This approach is based on secondary outcome analysis of patients enrolled in randomized controlled trials of chronic transfusion support.[32,33]
- Transfusion is not indicated as *treatment* of uncomplicated acute vaso-occlusive pain episodes, or for treatment of chronic pain syndromes (e.g., avascular necrosis, osteomyelitis, neuropathic pain).[15,34]

D2. Priapism (see Part II, section 10 on Priapism)

- Case series reports[35] and literature reviews[36] suggest that transfusion is of little benefit for priapism, and may be complicated by ASPEN syndrome (Association of SCD, Priapism, Exchange Transfusion and Neurologic events).
- Transfusion should only be considered in cases lasting over 4 hours that are unresponsive to aspiration of blood from the corpora cavernosa and irrigation with dilute epinephrine, and when surgical intervention (shunting and prosthesis) is either ineffective or not immediately available.[36]

D3. Ulcers (see Part II, section 12 on Skin Ulcers)

- The principal management of malleolar ulcers include skin protection, infection control, debridement, compression bandages and wet-to-dry dressings. Ulcers that do not respond to these treatments within 6 months may benefit from other modalities, including blood transfusion, although evidence of benefit is primarily anecdotal.[37,38]

D4. Pregnancy (see Part III, section 2 on Contraception, Pre-conception Counseling and Pregnancy)

- As long as adequate pre-natal care is provided (e.g., bi-weekly obstetrical assessment, switching to weekly in the last month), transfusions may be withheld in the absence of medical or obstetrical emergency without worsening of perinatal outcomes. Chronic transfusion support, however, can decrease the incidence of sickle complications in the mother, and may be considered in pregnant women with a history of frequent pain crises, given the contradiction to hydroxyurea during pregnancy.[32]
- Transfusion support may also be considered for pregnant patients with significant comorbidities (chronic renal, pulmonary, or hepatic disease), history of recurrent fetal loss, and in patients with either multigestational pregnancy or evidence of chronic fetal distress/intrauterine growth retardation.[15]
- Simple transfusion to improve oxygen carrying capacity is also advised, for fetal indications, in pregnant women with hemoglobin <60 g/L.[38]

E. Transfusion Complications

E1. Delayed Hemolytic Transfusion Reactions

- Without prophylactic phenotypic matching, 30% of transfused patients with SCD will develop alloantibodies – two thirds of them directed towards the C, E and Kell (K1) antigens.[39]

- As 30% to 50% of these antibodies will be undetectable on retesting within the year, patients may be re-challenged inadvertently with subsequent transfusions, resulting in high rate of delayed hemolytic transfusion reactions.[10]
- Delayed hemolysis manifests 1 week to 1 month after transfusion by worsening of hemolytic indices accompanied by new alloantibody in patient plasma (detected by blood group and screen) and/or on patient's RBCs (detected by direct antiglobulin test).
- Patients often present with symptoms typical of a vaso-occlusive pain episode. In some cases, delayed hemolytic transfusion reactions may progress to hyperhemolysis (see below).

E2. Hyperhemolysis

- Hyperhemolysis is defined as post-transfusion RBC destruction accompanied by a fall in Hb to below pre-transfusion levels. Hemolytic indices are increased from baseline, occasionally accompanied by relative reticulocytopenia.[40]
  - Delayed: occurs between 1 and 4 weeks following transfusion, and is often accompanied by new RBC antibodies
  - Acute: occurs less than 7 days after transfusion, often with no new antibodies detectable
  - Enhanced hemolysis appears to involve both transfused and autologous RBCs, and may be exacerbated by further transfusion of even crossmatch-compatible/antigen-negative RBCs.
- Avoid further transfusions if at all possible and treat with IVIG 2 g/kg over 2 to 5 days, accompanied by high-dose steroids (e.g., prednisolone 1 mg/kg/d x 7 days). Consider a brief course of erythropoietin if relative reticulocytopenia is found.[41]

E3. Hyperviscosity

- Be aware of hyperviscosity if sudden-onset hypertension is observed during or shortly after transfusion, accompanied by signs of congestive heart failure and profound alterations in mental status, including stupor, coma, seizures, or features of intra-cerebral infarct or hemorrhage.[42]
- Risk increases if Hb is transfused above 100 to 110 g/L in patients with SCD and HbS% >25%, particularly if the patient is dehydrated and hypoxemic.[3] Hyperviscosity may also occur secondary to autotransfusion following transfusion support of sequestration crises.
- Manage with emergent phlebotomy.

E4. Transfusional Iron Overload (see Part II, section 14 on Iron Overload)

- Each transfused unit of RBCs delivers 200 to 250 mg of iron; in the absence of blood loss or therapeutic phlebotomy, only ~1 mg of iron lost per day. Significant iron overload is therefore likely after repeated simple transfusion. Selecting fresh RBCs (<7 days old) may slow iron loading in chronically transfused patients to a small degree. Exchange transfusions may more effectively mitigate or even reverse iron loading.[43]

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