2. Transfusion Support in Thalassemia

Principles

- To promptly identify the indications to start blood transfusion in thalassemia patients
- To understand the rate and frequency of transfusion in thalassemia patients
- To understand the risk of blood product transfsuions

Recommendation

- Patients with beta-thalassemia major (including more severe forms of HgbE/ß-thalassemia) require transfusion support to prevent life-threatening anemia, which usually first appears by age 4-6 months and then steadily progresses.
- Maintaining a nadir hemoglobin of approximately 90-100 g/L is necessary to prevent disease related complications.
- The decision to transfuse a patient with thalassemia intermia should not be based purely on their hemoglobin level.
- Routine and specialized transfusion requirements needs to be followed as per Canadian Blood Services (CBS) guidelines.

Background

Beta-thalassemia major

- Patients with beta-thalassemia major (including more severe forms of HgbE/ß-thalassemia) require transfusion support to prevent life-threatening anemia, which usually first appears by age 4-6 months and then steadily progresses. Without regular transfusions, 85% of patients will die before the age of five years[31]. The secondary goal of transfusion, however, and one which requires an even more intensive degree of support, is suppression of ineffective erythropoiesis and the accompanying hypertrophy of myeloid bone marrow that occurs with it. At its extremes, this myeloid hypertrophy may be 10-20 times higher than normal, resulting in bony pain, low bone density, progressive skeletal deformities, and extramedullary erythropoiesis[32]. This latter condition in turn can exacerbate hepato-splenomegaly and promote the formation of benign tumors with associated mass effect (eg., spinal nerve compression).
- Previous studies in patients with beta thalassemia major have established that maintaining a nadir hemoglobin of approximately 90-100 g/L through regular blood transfusions will maintain the patient's erythoid mass at only 1-4x normal[33], which is generally adequate to prevent growth retardation, extramedullary hematopoiesis and dysmorphic bone changes.[34]
- Transfusing to achieve maintain at a Hgb higher than 100 g/L (aka "supertransfusion") will generally only result in more rapid iron loading[35] and in most cases should only be pursued as a short-term strategy to treat extramedullarly hematopoietic pseudotumours. In patients with beta thalassemia major there is insufficient evidence to support the use of higher transfusion thresholds than 100 g/L on the basis of comorbid cardiac disease.
- When transfusing to promote regression of extramedullary hematopoietic pseudotumours consideration must be given to the age of the masses, as over time many will undergo fatty replacement and will be unlikely to shrink in response to aggressive transfusion support.[35] Transfusion protocols that have been demonstrated to effectively shrink ectopic masses of bone marrow may require the administration of up to 2-4 units of RBCs per week over a period of months and will predictably lead to very rapid accumulation of iron.[36] Other modalities such as hydroxyurea, targeted radiotherapy, or rarely surgery, should therefore also be pursued wherever feasible.

Beta-thalassemia intermedia

- Distinguishing a patient with beta thalassemia major from beta thalassemia intermedia is not always straightforward in infancy and monthly monitoring of hemoglobin levels may be required, although genetic studies can be of assistance in predicting the clinical phenotype that will eventually emerge. By conventional definition, patients with beta thalassemia intermedia will require no more than 8 units of RBCs per year for adult patient to maintain a tolerable hemoglobin level.
- Without transfusion support, most patients with beta-thalassemia intermedia (including moderate severity HgbE/ß-thalassemia) will maintain a hemoglobin in the 70-100 g/L range, and transfusion may only be necessary if the hemoglobin transiently drops below the patient's usual baseline, as may occur during acute illness, pregnancy, hemorrhage or in the setting of progressive hypersplenism. Nonetheless, patients with beta-thalassemia intermedia are only able to maintain a tolerable hemoglobin without chronic transfusion support via significant erythroid hypertrophy accompanied by high rates of hemolysis. As a result, untranfused beta-thalassemia intermedia patients, even if able to maintain a hemoglobin level adequate for normal daily function, are still at increased risk of other long-term chronic comorbidities, including extramedullary hematopoietic pseudotumors, growth impairment, osteoporosis, dysmorphic bone changes, hepatosplenomegaly, pulmonary hypertension, pigment cholelithiasis, leg ulcers, and both venous and arterial thrombotic complications.[37] In addition, in comparison to those with beta-thalassemia major, untransfused patients with beta-thalassemia intermedia are at increased risk of developing a pseudoxanthoma elasticum-like condition.[38]
- Thus, the decision to transfuse a patient with thalassemia intermia should not be based purely on their hemoglobin level, particularly if the hemoglobin level has been augmented through interventions such as splenectomy, hydroxyurea, or erythropoietin: at any hemoglobin level, patients with beta thalassemia intermedia generally have greater degrees of erythroid hypertrophy than patients with beta thalassemia major.[33] Monitoring for skeletal abnormalities in these patients is particularly important in the pre-pubertal period so as to avoid the development of permanent deformity.[39] However, many of other complications have a delayed onset (often not becoming apparent until the third decade of life) and therefore the degree of transfusion support offered to patients with beta thalassemia intermedia requires lifelong monitoring of their clinical phenotype. Once a patient begins manifesting complications of erythroid hypertrophy and/or chronic hemolysis, transfusion support should be considered even if the steady state hemoglobin remains > 70 g/L.
- Conversely, however, even a patient with a hemoglobin in the 50-70 g/L range does not necessarily require transfusion support if they are tolerating this degree of anemia well from a symptomatic standpoint and are not manifesting any of the above complications; this may be particularly true in patients with HgbE/ß-thalassemia, who often tolerate even severe degrees of anemia due to a right-shifted oxygen dissociation curve.[40] Caution should be exercised before immediately attributing non-specific concerns such as poor school performance or poor quality of life to the patient's hemoglobin level, particularly given the quality of life impact that regular transfusions (and associated need for iron chelation therapy) will themselves provide. For many patients with beta thalassemia intermedia (and other otherwise non-transfusion-dependent thalassemias) transient decreases in hemoglobin due to intercurrent conditions (eg., pregnancy, acute illness) may require temporary provision of transfusion support but should not be misinterpreted as indicating a need to initiate chronic transfusion therapy. Finally, if transfusions were initiated in response to due fall in height velocity during childhood, or for the prevention of bony changes, it may be reasonable to attempt a weaning off transfusions after maximum height has been achieved and fusion of epiphyseal plates is complete, although ongoing monitoring for the emergence of other complications will be necessary.
- Suggested guidelines for transfusion support of patients with beta thalassemia intermedia have been published[41] but ultimately the decision will still need to be made on a case-by-case basis. If routine transfusion is pursued, targeting an erythropoietin level less than 150 mU/L may be a more reliable strategy for achieving adequate erythropoietic suppression than relying on hemoglobin levels alone. It should be noted that suppression of reticulocytosis is not a reliable indicator of transfusion adequacy in patients with thalassemia.[33] Once initiated, consideration should be given to re-evaluating patient response to transfusion support after six months: if no benefit has been seen in either subjective symptoms or objective indicators of organ dysfunction then discontinuation of routine transfusion is reasonable, although a tapering schedule may be preferable to allow for recovery from erythropoetic suppression.

Alpha thalassemia

- Patients with alpha thalassemia minor (three functioning alpha globin genes) and trait (two functioning alpha globin genes) are generally asymptomatic. Patients with HgbH disease (only a single functioning alpha globin gene), however, may have a degree anemia that occasionally requires transfusion support. Patients with no functioning alpha globin genes (Hgb Barts disease) will die in utero of fetal hydrops without aggressive transfusion support and are therefore encountered very infrequently in clinical practice; if intrauterine transfusions can sustain a developing fetus until delivery, transfusion management should continue in the antenatal period as per patients with beta-thalassemia major. Detailed discussions of intrauterine transfusion protocols for Hgb Barts are outside the scope of these guidelines but have been published elsewhere.[42]
- Patients with deletional HgbH disease tend to have baseline hemoglobin that runs in the range of 90-100 g/L, which is sufficient for most patients to enjoy a near normal quality of life, and because HgbH disease generally does not result in a significant degree of ineffective erythropoiesis, maintaining this baseline hemoglobin level does not generally incur the same complications that a patient with ß thalassemia intermedia might develop at the same hemoglobin level. Thus, transfusion is only required if the hemoglobin temporarily falls below a threshold generally required for adequate functioning (eg., Hgb < 70-80 g/L). This may occur during surgery or other episodes of blood loss, pregnancy, hypersplenism, aplastic crises (eg., infection with Parvovirus B19) or in the face of an oxidative stress that triggers increased hemolysis (eg., infection, fever, ingestion of oxidative drugs). These episodes are usually short-lived but may result in an abrupt fall in hemoglobin by as much as 30 g/L, and shock or organ failure may develop unless prompt transfusion support is provided.[43]
- Patients with non-deletional HgbH disease, however, tend to have lower baseline hemoglobin levels (eg., 70-80 g/L) and are more likely to require transfusion support at an earlier age.[11] Non-deletional HgbH disease diseases are often accompanied by an hemoglobin variant (eg., Hgb-Constant Spring) and the relative instability of this hemoglobin variant may further exacerbate the patient's baseline hemolysis and, with it, the risk of hepatosplenomegaly and gallstones.[44] Other examples of non-deletional HgbH disease include HgbH-Quong-Sze and HgbH-Pakse.
- Rarely, patients with non-deletional HgbH may develop a degree of ineffective erythropoiesis that results in comorbidities similar to those seen in ß-thalassemia intermedia (eg., skeletal abnormalities, extra-medullary hematopoiesis, iron overload). It is generally accepted, however, the primary determinant of anemia in HgbH patients is hemolytic anemia[45] and thus in most cases the goal of transfusion is not to suppress signs and symptoms of erythroid hypertrophy but to achieve a minimum hemoglobin level necessary to prevent acute organ dysfunction (eg., if hemoglobin falls below 50 g/L) and to provide freedom from significant fatigue (eg., when Hgb falls below 70 g/L).

Routine and Specialized Transfusion Requirements

Group, Screen and cross match

Each sample collected from a transfusion recipient must be tested for ABO and Rh groups and should be screened for clinically significant red cell antibodies. With the exception of emergency situations (eg., major hemorrhage or a life-threatening degree of anemia), all transfused RBCs should be crossmatched to detect any incompatibility between the donor and recipient. Approximately 15-20% of thalassemia will become sensitized to RBC minor blood group antigens[76,77] with even higher rates observed amongst patients of Asian descent.[78] A large proportion of these antibodies will be against the C, E, c, e and K antigens, and prophylactic matching for these antigens has been shown to decrease the overall rate of alloimmuization significantly.[76,79] . In keeping with other published recommendations, prophylactic matching for C, E, c, e and K antigens is therefore recommended.80 To facilitate this, and to assist in the investigation of any new antibody specificities that may also develop, patients should be phenotyped for all common clinically significant antigens (D,C,E,c,e,K,k,Fya,Fyb,Jka,Jkb,S,s) prior to their first transfusion or, if not possible, by genotyping using a licensed testing platform.

Blood component production

RBCs provided by licensed manufacturers in Canada meet the general requirements required by the Thalassemia International Federation and are therefore acceptable for use in Canadian patients.[46] For patients travelling abroad, however, clinicians should ensure that any blood products provided in other jurisdictions are also manufactured in accord with the following:[47]

- Blood donors are voluntary and non-remunerated.
- Donations are processed, stored and distributed under the aegis of a rigourous quality assurance program.
- Testing for infectious disease includes highly sensitive assays for HIV, hepatitis B and hepatitis C, with additional testing for other clinically-significant transfusion-transmissible diseases that are known to occur within the local population (eg., West Nile Virus, Chagas Disease).
- Each unit of RBCs is collected and stored under conditions that assure the hematocrit is kept less than 80% at all times, the hemoglobin content kept above 40 g/L at all times, hemolysis kept less than 0.8% at time of expiration, and sterility is maintained throughout.

Notably, the provision of directed blood donations (eg., from parent to child) greatly increases the cost and complexity of blood product provision[48] and places the recipient at increased risk of both transfusion-associated graft-versus-host-disease[49] and transfusion-related acute lung injury.[50] For these reasons, directed donations are discouraged unless it proves impossible to source non-directed blood due to a high degree of patient sensitization to RBC minor blood group antigens.

Irradiation and Cytomegalovirus (CMV)-testing

Cellular blood products should be irradiated with gamma rays to prevent transfusion-associated graft-versus-host-disease in at-risk recipients; the recommended dose is 25 Gy directed towards the centre of the blood product.[58] At-risk recipients include but are not limited to the following:

- intrauterine transfusions.
- recipients of cellular blood components known to be from a blood relative.
- recipients who have undergone hematopoietic progenitor cell (stem cell) transplantation.
- recipients of HLA-selected platelets or platelets known to be HLA homozygous.
- Asplenia in thalassemia patients is not sufficient to justify blood product irradiation.

CMV-sreonegative blood products are generally not indicated in routine transfusions in thalassemia patients unless patient is pregnant, considered for stem cell transplant or in uetro transfusion is indicated.

Blood Product Administration

Informed consent

Documentation that the patient (or their surrogate decision-maker) understands the nature of the blood component that is being offered to them, including the associated risks, benefits, and alternatives, should be maintained in the clinical record[74]. The consent process should be repeated prior to the administration of further transfusion support. Obtaining informed consent is the responsibility of the individual proposing the treatment.[81]

Patient monitoring

To facilitate early detection of acute transfusion reactions, vital signs should be recorded before, during and following a blood transfusion. Close observation and a slower infusion speed is particularly advised for the first 15 minutes of a transfusion[36] Patients should only be transfused while under the care of a healthcare worker (eg., a physician or nurse) and, ideally, with immediate access to resuscitative equipment. Provision of transfusion support after-hours and on weekends is an important consideration in patients who are in school full-time or have regular working hours.

Transfusion dose

For outpatients, it is convenient to set the dose of blood administered to be large enough to allow a repeat transfusion to be delayed by approximately 3-4 weeks while still maintaining the pre-transfusion hemoglobin within target range. It is preferable for most patients to be transfused a fixed quantity of blood at a fixed schedule, making adjustments in response to pre-transfusion hemoglobin levels that are persistently out of range, rather than waiting until the pre-transfusion hemoglobin falls within target range and then ordering a transfusion.

In young children it may be difficult to attain a target pre-transfusion hemoglobin with reasonable precision without ordering blood in weight-adjusted doses (typically 5-15 mL/kg). One recently-proposed formula for precise dosing based on baseline and target hemoglobin levels is listed below:[82]

[Desired – actual Hgb in g/L]/10 x weight [kg] x 3[Hct of transfused unit] = mL to be administered

Notably, when applying the above formula to RBCs with a standard Hct of 0.6, the difference in blood volume required to change the target Hgb by 10 g/L increases to approximately 300 mL once the patient's weight exceeds 50 kg. As this is the approximate volume of a unit of RBCs in optimal additive solution, maintaining a pre-transfusion Hgb in the range of 90-100 g/L in thalassemia patients larger than 50 kg can therefore be achieved with reasonable precision by ordering the transfusion dose in units rather than in mL/kg; ordering in units will decrease wastage of untransfused blood.

If the total transfusion dose necessary to achieve the target hemoglobin is excessive, consideration may be given to splenectomy, a procedure which can decrease transfusion requirements in thalassemia patients by approximately 30%.[53] As splenectomy itself carries risks, an excessive transfusion dose should be defined restrictively, as follows:

- The transfusion dose results in a degree of iron loading which cannot be chelated without inducing significant toxicity.
- The transfusion dose requires either a larger fluid volume than can be accommodated by either pre-transfusion diuresis, plasma-volume reduction, or by administering smaller doses at more frequent intervals.

The above criteria are more likely to be met when the total annual volume of blood administered exceeds 200 mL/kg per year of pure red blood cells (ie., 250-275 mL/kg per year of RBCs in optimal additive solution)[84], which for a 70 kg patient corresponds to 5-6 units per month. However, when this threshold is reached, particularly in patients whose epiphyseal growth plates have already fused, consideration may also be given to decreasing the transfusion dose via the adoption of slightly lower pre-transfusion Hgb targets (eg., 80-90 g/L). Careful monitoring for signs and symptoms of under-transfusion (eg., bony pain, progressive hepatosplenomegaly, pulmonary hypertension) are required if opting to take this approach.

Pre-medication

While there is no evidence from clinical trials that pre-medication decreases the risk of acute transfusion reactions, it is a reasonable intervention to consider in patients with recurrent reactions so as to at least attenuate their severity.[85]

Rate of infusion

To minimize transfusion reactions, blood products should be administered at the slowest feasible rate of infusion (to a maximum of four hours per unit between removal from storage and completion of infusion). The maximal rate of infusion should be determined for each individual patient, taking into consideration the total volume to be administered and the patient's capacity to tolerate a fluid challenge.

Transfusion Reactions

Transfusion reactions that could occur in thalassemia patients are similar to others. These include acute, chronic reactions and iron overload. CBS has an extensive review on management and approach to each reaction.