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Update article

## Transfusing children with hemoglobinopathies

### La transfusion des enfants atteints de maladies de l'hémoglobine

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#### ABSTRACT

Thalassemia and sickle cell disease (SCD) are among the most common inherited diseases worldwide. Red blood cell transfusion is a cornerstone of their treatment, but its indications have significantly changed over the past years. New therapies are emerging in both syndromes: among them, hematopoietic stem cell transplantation is now routinely proposed, and gene therapy has shown promising preliminary results.

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#### R É S U M É

Les syndromes thalassémiques et drépanocytaires font partie des maladies génétiques les plus fréquentes au monde. La transfusion de concentrés érythrocytaires est un traitement majeur, dont les indications ont évolué au cours des dernières années. De nouveaux traitements ont également fait leur apparition : la greffe de cellules souches hématopoïétiques est désormais proposée en pratique courante et la thérapie génique a montré des résultats préliminaires prometteurs.

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Thalassemia and sickle cell disease (SCD) are the most frequent genetic diseases in the world [1]. Access to safe and sufficient blood supplies is a major prognostic factor, but unfortunately, countries with high prevalence of these diseases are most often characterized by low access to safe transfusion [2].

### 1. Thalassemic syndromes

Their severity is related to the degree of imbalance between  $\alpha$ - and  $\beta$ -globin chain production. Some thalassemic mutations

totally suppress the production of  $\alpha$ - or  $\beta$ -globin chains (they are called  $\alpha_0$  and  $\beta_0$  mutations respectively), whereas others affect less severely globin chain production (they are called  $\alpha+$  and  $\beta+$  mutations respectively). During the last decade, major progress has been made in understanding the pathophysiology of thalassemia [3]. In  $\beta$ -thalassemia, excess  $\alpha$ -chains sequester cytosolic heat shock protein 70, which becomes unable to protect erythroid transcription factor GATA 1 from cleavage. As a result, lack of GATA 1 protection leads to ineffective erythropoiesis. Furthermore, excess  $\alpha$ -chains induce Reactive Oxygen Species formation, which contributes to ineffective erythropoiesis via GDF11 activation, with a cascade of complications such as suppression of hepcidin production and iron overload. Given the multiplicity of mechanisms involved, there is a wide variation in clinical and biological expression of thalassemic syndromes, ranging from

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severely affected patients requiring lifelong monthly red blood cell (RBC) transfusions for survival (these syndromes are called Transfusion-Dependent Thalassemias (TDT)), to patients who do not require monthly RBC transfusions, although they may need occasional ones (these syndromes are called Non-Transfusion-Dependent-Thalassemia (NTDT)). NTDT encompasses 3 forms, namely  $\beta$ -thalassemia intermedia, mild and moderate forms of hemoglobin E/ $\beta$ -thalassemia, and hemoglobin H disease. Recommendations for transfusing children with TDT are consensual and have not changed significantly in recent years. Transfusions of 15–20 ml/kg of erythrocyte concentrate every 3 to 4 weeks aim to maintain hemoglobin level constantly over 9 g/dl, which improves growth and activity, and reduces hepatosplenomegaly, bone deformities, and extramedullary hematopoiesis [4]. Effective iron chelation is mandatory and remains challenging even if oral chelators are now available. Over the last years, chronic transfusion programs have become more frequently recommended for NTDT [5].

Importantly, other therapies have emerged as alternatives to RBC transfusion. Hematopoietic stem cell transplantation is curative but is limited by a relative scarcity of HLA-matched siblings. Outcomes of gene therapy vary according to genotypes and excellent results have been observed in non- $\beta_0/\beta_0$  patients [6]. This finding has recently led the European Medical Agency to recommend “granting a marketing authorization in the European Union for adult and adolescent patients 12 years and older who do not have a  $\beta_0/\beta_0$  genotype and have no matching donor for a stem cell transplant”. Drug therapies aim to decrease or suppress transfusion needs. Hydroxyurea has been used for several years and may be effective in patients with thalassemia intermedia [7]. Besides, several new approaches are developing, either inducing iron restriction to erythropoiesis, or trying to overcome maturation blockade with TGF- $\beta$  ligand traps, which seems very promising. Here again, the mildest forms are those with the best response [8].

## 2. Sickle cell disease

RBC transfusion is a keystone in the management of SCD and 90% of adult patients have received at least one transfusion [9]. The objectives are either to restore hemoglobin level up to baseline value in order to increase oxygen-carrying capacity, which can be achieved by simple transfusion, or to replace rigid sickle RBCs by deformable RBCs, which can be done through exchange transfusion. Exchange transfusion combines venesection and RBC transfusion and can be performed manually or as an automated procedure with an erythrocytapheresis machine. It reduces hemoglobin S (HbS) percentage without increasing excessively hematocrit, thus avoiding hyperviscosity and deleterious reduction of oxygen distribution in tissues.

## 3. Indications for RBC transfusion

There are very few randomized studies on RBC transfusion, and most recommendations are based on professional consensus.

### 3.1. Emergent RBC transfusion

#### 3.1.1. Acute anemia

All patients with SCD have usually well tolerated chronic hemolytic anemia. Acute exacerbation of chronic anemia may lead to symptoms of hypoxia and hypoperfusion, requiring simple RBC transfusion. Common causes are acute splenic sequestration, Parvovirus B19-associated transient red cell aplasia, and increased hyperhemolysis during a vaso-occlusive crisis or an infectious episode. Key points for deciding to transfuse a patient with SCD

are hemoglobin level (RBC transfusion is rarely necessary when hemoglobin level is  $> 6$  g/dl) relative to baseline, clinical tolerance of anemia, reticulocyte counts, and existence of previous immunohematological complications or rare blood group. RBC transfusion aims to bring hemoglobin level up to its baseline value.

#### 3.1.2. Organ failure

Choice between manual or machine exchange transfusion depends on:

- the severity of the complication (stroke, severe acute chest syndrome, and acute hepatic failure are life-threatening; priapism is extremely painful: in these conditions, a rapid depletion of HbS by erythrocytapheresis is recommended with an objective of HbS  $< 30\%$  (threshold based on clinical experience);
- hemoglobin level (when  $> 8$ – $9$  g/dl, exchange transfusion is preferable in order to avoid hyperviscosity);
- local facilities (i.e. are a machine and a trained team available?).

#### 3.1.3. Preoperative transfusion

A randomized study of RBC transfusion versus observation in SS and S $\beta_0$  patients showed that non-transfused patients experienced more complications (acute chest syndromes mostly) than transfused ones [10]. Transfusion should be discussed case by case in patients with milder genotypes (SC and S $\beta_+$ ) and in patients with a past history of alloimmunization.

## 3.2. Chronic RBC transfusion

Indications for chronic transfusion in children most frequently relate to cerebral vasculopathy. Children who had a stroke are at very high risk for recurrence, and regular RBC transfusions (or exchange transfusions depending on hemoglobin level) are efficient in preventing a secondary stroke, although the efficacy of this strategy has not been demonstrated by randomized studies. Children at highest risk for presenting a first stroke are screened with transcranial Doppler (TCD) measuring cerebral velocities, and chronic transfusion is indicated if velocities are abnormal. Transfusion program may be stopped after at least one year and replaced by hydroxyurea in children with normalized TCD and normal cerebral magnetic resonance imaging (MRI) [11]. Chronic transfusion is also proposed to children with recurrent painful crises or acute chest syndromes non-responding to hydroxyurea, and to children with recurrent splenic sequestrations before splenectomy [12].

An important complication of RBC transfusion is alloimmunisation, which is the consequence of discrepancies in blood group antigens between donors, mostly of European descent, and patients, mostly of African descent. Delayed hemolytic transfusion reactions can occur and are often life-threatening [13].

Iron overload must be prevented in children on chronic transfusion because they are at risk of developing hepatic complications. Assessment of iron overload may be difficult using serum markers because chronic inflammation also increases ferritin levels; MRI quantification of liver iron content is therefore helpful in this setting. Erythrocytapheresis procedures limit the amount of iron provided by chronic transfusion programs and can help reduce the need for chelation.

Another major treatment of SCD is hydroxyurea, which decreases hemolysis, increases hemoglobin level, and reduces transfusion needs [12]. Hematopoietic stem cell transplantation is curative and because its safety is increasing, it is now proposed to all children with very symptomatic disease who have an HLA-identical sibling donor [14]. One child has recently benefited from a gene therapy [15]. Indications for this innovative treatment

remain to be debated, as it exposes children to myelo-ablative conditioning.

### Disclosure of interest

M. de Montalembert, scientific advisor for Addmedica, Novartis, and Blue Bird Bio.

The other authors declare that they have no competing interest.

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