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Saliou Diop France Pirenne

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## Transfusion and Sickle cell anemia in Africa

Saliou Diop<sup>1</sup>, France Pirenne<sup>2</sup>

- 1- Service d'Hématologie Université Cheikh Anta Diop, Centre National de Transfusion sanguine BP 5002  
Dakar, Sénégal
- 2- Université Paris Est Créteil, INSERM U955, Etablissement Français du Sang, 94000, Créteil, France

Corresponding author : Saliou Diop, email: [saliou.diop@ucad.edu.sn](mailto:saliou.diop@ucad.edu.sn)

### Abstract:

Sickle cell anemia (SCA) is the commonest life-threatening genetic disorder in tropical regions, particularly in sub-Saharan Africa. It has been estimated that between 50-90% of SCA children will die in Africa before the age of 5, corresponding to a number of 150,000-300,000 annual SCA child deaths, which represents 5-10 % of total child mortality. Transfusion support remains an essential component in the management of patients with SCA and has made a significant contribution to improving patient morbidity and mortality. In Africa where the majority of patients with SCA reside, many blood transfusion challenges remains, including shortage of blood supplies, risks related to infectious and immunologic potential side effects and limitation on the diagnosis and management of post-transfusion iron overload. The proportion of transfused SCA patients varies from different studies, between 30% and 90%. This variation can be related to environmental factors, disease genetic factors and other factors including the low availability of blood, difficulties in accessing to health care and inadequacies of the transfusion system. Because blood transfusion therapy is an integral component of the management of SCA, improved efforts and strategies to overcome these challenges and optimize blood transfusion practices are needed in African countries.

Key words: Sickle cell anemia –blood transfusion- alloimmunization- Africa

La drépanocytose est certainement la maladie génétique responsable d'une plus grande mortalité dans les pays tropicaux, en particulier en Afrique subsaharienne. On estime qu'entre 50 et 90 % des enfants atteints de drépanocytose mourront en Afrique avant l'âge de 5 ans, ce qui correspond entre 150 000 et 300 000 décès annuels d'enfants atteints, représentant 5 à 10 % de la mortalité infantile totale. Le support transfusionnel demeure un élément essentiel dans

la prise en charge des patients et a apporté une contribution significative à l'amélioration de la morbidité et de la mortalité des drépanocytaires. En Afrique, où résident la majorité des patients atteints de drépanocytose, de nombreux défis liés à la pratique transfusionnelle demeurent, notamment la pénurie d'approvisionnement en sang, les risques liés aux effets secondaires infectieux et immunologiques potentiels et la limitation du diagnostic et de la prise en charge de la surcharge en fer après transfusion. La proportion de patients drépanocytaires transfusés varie de 30% à 90% selon les différentes études. Cette variation peut être liée à des facteurs environnementaux, des facteurs génétiques de la maladie, des facteurs génétiques de la maladie mais aussi à d'autres facteurs, notamment la faible disponibilité du sang, les difficultés d'accès aux soins de santé et les insuffisances du système transfusionnel. Étant donné que le traitement transfusionnel fait partie intégrante de la prise en charge de la drépanocytose, des efforts et des stratégies améliorés pour surmonter ces défis et optimiser la pratique transfusionnelle sont nécessaires afin de contribuer à l'amélioration de la morbidité et de la mortalité de cette maladie en Afrique subsaharienne.

Mots clés : Drépanocytose – Transfusion sanguine – allo immunisation - Afrique

## **Introduction**

Sickle cell anemia (SCA) is an inherited blood disorder caused by mutations in the  $\beta$ -globin gene that lead to the production of abnormal forms of the hemoglobin  $\beta$ -subunit. It is the commonest life-threatening genetic disorder in tropical regions, particularly in sub-Saharan Africa, but also in India, the Mediterranean basin and the Middle East [1,2]. Sickle cell disease is also present in the United States among African Americans and in Europe due to migration of substantial populations from high prevalence areas during these last 50 years [3].

Transfusion support remains an essential component in the management of patients with SCA and has made a significant contribution to improving patient morbidity and mortality [4].

Red cell transfusions are used in the acute and chronic management of many complications related to SCA. In patients with SCA, transfusion of normal RBCs is intended to correct the oxygen-carrying capacity, diluting circulating sickle RBCs, and suppress their endogenous production, reducing the proportion of sickle hemoglobin (HbS) concentration, with subsequent improvement in blood viscosity and microcirculatory perfusion [5].

In Africa where the majority of patients with SCA reside, many blood transfusion challenges remains, including shortage of blood supplies and the risks related to infectious and immunologic potential side effects [6]. In this review, we will discuss the burden of SCA in

Africa, the current practice of blood transfusion for the management of SCA. We will also highlight the current transfusion challenges and the different perspectives and strategies for improvement in this region.

### **The Burden of Sickle cell anemia in Africa**

An estimated 300,000–400,000 babies with SCA are born every year, about 75% of them across a geographical band in Africa within the sicklemic belt of Lehmann, stretching from Senegal to Madagascar, mirroring the continent's malaria endemicity [7]. The prevalence of HbS trait is 5-20% in West Africa and reaches up to 40% in Central Africa with over 1% of all newborns having SCA [8].

It has been estimated that between 50-90% of SCA children will die in Africa before the age of 5, corresponding to a number of 150,000-300,000 annual SCA child deaths, which represents 5-10 % of total child mortality in Africa [2, 9].

Advances in the management of the disease in children, as well as the observed epidemiological transition, have resulted in a higher number of adult patients with sickle cell disease who require expensive, specialized care related to chronic complications of the disease like stroke, bone necrosis, renal failure, heart, pulmonary and other organ diseases.

Despite this rather bleak picture, it must be recognized that significant progress has been made in recent years to enable earlier diagnosis of the disease and better management. These include better political engagement following strong advocacy from civil society, the implementation of pilot neonatal screening programs in several African countries [10, 11], the introduction of preventive measures to reduce deaths before the age of 5, a quarter of which is due to infections, a greater availability of specialized Sickle cell disease comprehensive care centers and better trained staff. Furthermore, availability of an electricity-free bedside point of care device requiring only 1 to 5  $\mu\text{L}$  of blood from a fingerstick and with high sensitivity and specificity, allow easier diagnosis especially in newborns [12, 13].

### **Current transfusion practice in SCA in Africa**

Blood transfusion is an essential component in the care of patients with sickle cell disease (SCD), but it might be associated with serious acute and delayed complications.

Intermittent RBC transfusion is indicated for episodes of acute anemia occurring with splenic sequestration, transient aplastic crisis, hyperhemolytic crisis, and other acute complications

such as acute chest syndrome (ACS), acute stroke, acute sickle hepatopathy, multisystem organ failure, and perioperative management [14]. Chronic transfusion is indicated for the primary and secondary prevention of stroke, recurrent splenic sequestration, recurrent ACS, and frequent refractory painful crises that do not response to hydroxyurea therapy [15].

Blood transfusion can be administered by a simple or exchange transfusion. Simple transfusion is more frequently used for acute transfusion, as it is more convenient and easier to administer, while exchange transfusion (automated or manual) is used in case of higher pretransfusion hemoglobin, at risk of hypervolemia, and in clinical conditions requiring rapid reduction in the proportion of HbS and hyperviscosity [16],

In Africa, the proportion of transfused SCA patients varies from different studies, between 30% and 90% [17, 18]. It must be said that this variation can of course be related to environmental factors and disease genetic factors (haplotype, Hb F levels etc.) Other factors include the low availability of blood, difficulties in accessing to health care as patients often have to pay out of pocket for this, and the inadequacies of the transfusion system.

While in Europe and the USA the main indications of transfusion in sickle cell patients are represented by chronic transfusion program, especially in the context of cerebral vasculopathy, blood transfusion is mainly used for acute anemic complications in Africa, especially in children who suffer from infections such as malaria, splenic sequestration or acute hemolysis.

Simple transfusion is the most commonly used modality, although there are some experiences reporting practice of red cell exchange transfusion [19, 20], using manual technology because of limited availability of apheresis machines.

### **Challenges with transfusion in SCA in Africa**

Inadequate blood supply is one of the biggest challenges when dealing with transfusion in SCA in Africa. In a study from Nigeria [21], 78% of hospitals declared they were unable to transfuse patients regularly due to blood scarcity and packed red blood cells were available in only 45%. In the 2016 WHO report on blood safety and availability [22], the 46 countries in the WHO African Region collected for only about 4% of global donations, though these countries are home to around 13% of the global population; the proportion of voluntary non-remunerated donations was only 67%, and the percentage for processing blood into components was 69 % in the African Region.

Increased risk of transfusion transmitted infections (TTI) is a limiting factor as the prevalence of TTI is high in the general population, and safety measures as leukodepletion of cellular products, and infectious disease screening taken to reduce the residual risk of transmission are not always the most effective [23].

Individuals with sickle cell anemia are at high risk of developing complications of blood transfusions, including iron overload, auto- and alloimmunization to red cell and human leukocyte antigens, delayed hemolytic transfusion reactions, and hyper-hemolysis.

The prevalence of allo immunization in transfused SCA patients varies from 4 to 30 % in Africa [24]. Extended phenotypic matching beyond antigens of the Rh and Kell blood group systems, using either serologic or molecular methods, is a strategy to prevent alloimmunization [25] and these techniques are not routinely performed in Africa.

Chronic blood transfusion has a high risk of iron overload, although organ damage associated with this overload is less common than in thalassemia and in genetic hemochromatosis [26]. However, management of post-transfusion iron overload is very limited in Africa, due to the lack of the biologic and radiological tools to accurately diagnose this overload, and the high cost of its treatment

In summary, because blood transfusion therapy is an integral component of the management of SCA, improved efforts and strategies to overcome these challenges and optimize blood transfusion practices are needed in African countries.

### **Perspectives and strategies to improve transfusion in SCA in Africa**

In general, transfusion safety with regard to transfusion-transmitted infections (TTI) must be optimized in Africa, but this subject does not specifically concern sickle cell disease, except that these patients are more frequently transfused than the general population, and therefore more often exposed to TTI. Améliorer la disponibilité du sang en se basant sur une bonne politique de promotion du don de sang volontaire et bénévole permettra de réduire la dépendance au don de sang familial. Pour cela, des ressources additionnelles devraient être allouées au secteur de la transfusion sanguine en Afrique. Improving blood availability based on a good policy to promote voluntary and no remunerated blood donation will reduce dependence on family blood donation. For this purpose, additional resources should be

allocated to the blood transfusion sector in Africa. However, several indicators have improved in Francophone Africa Blood Services during the last past years. [27]

What is much more specific to sickle cell anemia is the risk of post transfusion alloimmunization, and the associated post transfusion hemolysis. Alloimmunization persists at a high level, despite a potential better phenocompatibility between patients and donors of the same origin decreasing the polymorphism between them, especially for the FY, JK and MNS blood groups.[24] The main causes are most likely the inflammation which promotes alloimmunization and which is associated with the acute transfusion indications for sickle cell disease (acute chest syndrome, vaso occlusive crisis), the absence of leukoreduction of the products, as whole blood is the major blood product used, and limited compatibility to the ABO-D group. [28] In a meta-analysis, antibodies of the Rhesus system represent 47% of the antibodies found. [24] However, there are no studies giving the incidence rates of the poor yields or of post-transfusion hemolysis associated with alloimmunization. In order to develop strategies to improve transfusion safety in Sub Saharan Africa, taking into account the limited resources in terms of equipment and reagents, the first step would be to evaluate the real burden of the consequences of allo immunization. As a general rule, in Sub Saharan Africa, the screening test and / or the serological cross-match are only carried out in patients who have a poor transfusion performance. The best approach would be at least to match patients for RH and K, perform a screening test or a serological cross match prior all transfusion in SCD patients.

Then, altogether, a first step would be to develop studies looking precisely to the hemolytic transfusions' reactions and poor yields, in SCA patients in Sub Saharan Africa, and then, adapt the transfusion protocols to the epidemiology of these reactions, and increase the accessibility to the adapted reagents and equipment.

A few collaborative frameworks are emerging [29] and we hope that these issues can also be included in the research themes.

Efforts will also need to be made to make iron chelators more accessible, to enable chronic transfusion programs to be implemented by reducing the risk of iron overload.

**Conclusion:** Sickle cell anemia patients are very often transfused and the risks associated with blood transfusion are multiplied in these patients. Improving the transfusion system will reduce morbidity and mortality among these patients with a positive impact on reducing the disease burden in Africa

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