Commentary

Black blood matters

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In Western countries, the number of persons affected by haemoglobinopathies, including sickle cell disease (SCD) and thalassaemia syndromes, is constantly increasing owing to migratory flows from the Middle East and Africa[1]. Blood transfusion remains a key treatment for many patients with haemoglobinopathies. However, selecting compatible units can be challenging, especially in the case of patients of Sub-Saharan (SSA) descent. In these populations, malaria has provided a major pressure favoring the selection of sickle cell trait and rare blood groups, conferring partial protection against *Plasmodium* infection.

In Europe, SSA natives and descendants are commonly transfused with blood collected from European donors, and therefore a mismatch of highly immunogenic red cell antigens occurs very frequently. Also, SCD patients are particularly susceptible to developing alloantibodies, favoured by inflammation and immune dysregulation associated with the disease. In previously transfused SCD patients, the frequency of alloimmunisation can be as high as 70%, predisposing them to life-threatening reactions and causing a progressive restriction of compatible donors[2].

To prevent alloimmunisation, it is now recommended that patients with SCD and transfusion-dependent thalassemia undergo extended RBC antigen profile by genotyping or serology at the earliest opportunity (optimally, before the first transfusion) and, whenever possible, receive RBC transfusions prophylactically best matched for ABO, Rh (C, E or C/c, E/e) Kell (K/k), Kidd (Jk^a/Jk^b), Duffy (Fy^a/Fy^b), and MNS (S/s) antigens[3]. However, to ensure matched red blood cells, a suitable number of donors of African ancestry need to be included in the donor pool. For example, a ccDee phenotype is present in 63% of SCD patients regularly transfused at our center, but only in 2.7% of Italian donors. Also, a Duffy null phenotype (Fya-/Fyb-) is present in the vast majority (94%) of SSA patients but nearly absent among Italian donors.

Lombardy is the largest Italian region, providing one-fifth of the national blood supply. It has the largest community of SSA citizens, around 300,000 in 2019, accounting for 3% of the whole population. Unfortunately, the efforts to increase the number of donations from SSA donors are frustrated by the high rate of deferrals. In the province of Lecco, a recruitment campaign was launched in 2012 within our Lombardy Rare Donor Programme (LORD-P) and fully supported by local SSA community leaders. The recruitment programme was conceived to widen Rare Blood Bank stores and promote social integration of African communities as well, thus complying to WHO Recommendations for health status control of foreign citizens[4]. The programme allowed us to recognize health conditions of foreign

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people settled in our territory, explore the level of their integration in social habits and health system, and lately implement dedicated pathways for those, deferred from blood donation, who needed additional investigations and treatment. Among those who were invited to donate, the acceptance rate was as high as 25%, and 212 candidates (81 females and 131 males, aged 18-65) were evaluated. Nevertheless, based on the current national directives, only 28 (13%) were suitable for donation, and the remaining 184 (87%) were deferred for one or more reasons. As described in **Table I**, 32 donors (15%) resulted positive for either HBsAg or anti-HIV. Not surprisingly, the frequency of isolated anti-HBc reactivity, a marker of occult HBV infection, and malaria semi-immunity

Table I - *Causes of deferral in apparently healthy candidate blood donors of Sub-Saharan African descent*

Positive donors	Number	%
HIV+	9/212	4.2
HBV+ (HBsAg+ and/or HBV nucleic acid +)	23/212	11
Anti-HBc+ (total)	140/212	70
Anti-HBc+ (in HBsAg–)	117/185	63
Malaria antibodies+	143/198	72
Negative partner of virus carrier	5/212	2

Table II - *Persistence of circulating malaria antibodies in 191 healthy citizens of Sub-Saharan African descent after settling in Italy (subjects have been considered once)*

Settled in Italy (years)	Number of anti-malaria positive subjects	Percentage of anti-malaria positive subjects
1-3	20/29	69
4-7	28/39	74
8-13	45/62	74
13-30	40/67	67

Table III - *Measures to improve the transfusion management of persons of African descent in European countries*

Health institution	Target population	Tasks
Blood establishments, hospital blood banks	SCD patients Patients with transfusion-dependent thalassaemia syndromes	• Perform blood typing on patients with haemoglobinopathies soon after diagnosis, possibly at birth • Refer blood specimens of newly diagnosed patients to reference laboratory for extended blood typing • Regularly update the red cell antibody profile of patients, especially after blood transfusions and pregnancies • Ensure that patients receive blood units best matched for clinically significant red cell antigens • Promote HBV vaccination • Whenever possible, programme blood transfusions or blood exchange to better ensure appropriate donor selection
	Donors of SSA descent	• Promote blood donation among communities of people of SSA descent • Accept candidate donors who have no medical or behavioural contraindication to donation and test negative for markers of major transfusion transmittable infection either by serology or nucleic acid testing • Refer blood specimens of donors of SSA descent to a reference laboratory for extended blood typing • Test blood donors for anti-HBc, Hb electrophoresis, G6PDH activity, and malaria serology • Independently of the results of the aforementioned tests, which must be taken into account, send rare blood units to the rare blood bank • Actively maintain the SSA donor pool
Regional reference laboratories and rare blood banks	Patients and donors of SSA descent	• Organize a database of red cell typing (by serology and/or molecular biology) of patients with haemoglobinopathies • Typing data will be valid for the subject's entire life-time • Implement and maintain an inventory of frozen rare blood units • Organise a national database of red cell typing (by serology and/or molecular biology) of rare blood donors supported by the ongoing update from regional co-ordinating centres • Match and release rare blood units to patients • If release of anti-HBc positive or anti-malaria positive rare blood units is necessary, consider approaches to mitigate the risk of post-transfusion infection (e.g., pathogen reduction techniques, anti-infective prophylaxis)

SCD: sickle cell disease; SSA: Sub-Saharan African.

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was high: 63% and 72% respectively. We also evidenced a long-lasting persistence of malaria antibodies, as documented in **Table II**. Despite rarely, such conditions are associated with transmission of HBV and *Plasmodium* to blood recipients and are thus considered a reason for donor deferral in almost all European countries[5-9].

The widespread persistence of occult HBV and malaria infections represent a bottleneck on recruitment of sub-Saharan blood donors, and this hampers programmes of sustainability of proper transfusion therapy for their countrymates. As illustrated in **Table III**, this issue deserves to be addressed with tailored counter-measures, carefully balancing transfusion safety and blood sufficiency. In our opinion, all SSA candidate donors who have no medical or behavioral contraindication and test negative for the main markers of transfusion-transmitted infections (i.e., HBsAg, anti-HCV, anti-HIV-1/2, and syphilis by serology and HBV DNA, HCV RNA and HIV RNA by nucleic acid testing) should be extensively typed for red cell antigens. Those with rare blood group phenotypes should be allowed to donate, even in the presence of isolated anti-HBc or a positive malaria serology. Registries of rare SSA donors should be used for on demand call to donation for specific patients. In addition, rare blood units could be stored frozen in Rare Blood Banks. Such units could be thawed and released for transfusion when the potential benefit outweighs the potential harm, as jointly assessed by the medical director of the Rare Blood Bank Programme and the clinician who is in charge of the patient. Whenever necessary, personalised patient management and monitoring could be decided, including the administration of antivirals, and/or anti-malaria prophylaxis. If licensed for whole blood application, pathogen reduction treatments will help to further reduce the infectious risk of these units. *In vitro*, the Mirasol system (based on riboflavin + ultraviolet light exposure) has been shown to be effective against *Plasmodium spp.*, HIV and HBV, the main infectious agents identified in SSA blood donors. In addition, a recent randomised trial demonstrated the safety and efficacy of this system in reducing post-transfusion malaria in African patients transfused with blood collected from parasitaemic donors[10-11].

Keywords: rare blood, sickle cell disease (SCD), sub-Saharan African (SSA), malaria, blood donation, pathogen reduction.

DISCLOSURE OF CONFLICTS OF INTEREST

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