Prevalence of alloantibodies in sickle cell patients worldwide

Development alloantibodies is a well-recognized phenomenon in sickle cell anemia and thalassemia patients. Nevertheless, there are no established statistics on the prevalence of alloimmunization worldwide. Since we have provided in an earlier section the prevalence of alloantibodies in the middle east with the most common antibodies formed, it is logical examine the distribution of this phenomenon worldwide.

In Europe, a Dutch paper examined the frequency of alloimmunization among 245 SCD patients and revealed that 18% of these had alloantibodies. Half of these patents developed alloantibodies before they received their 8^{th} unit. This study took into consideration the introduction of extended matching for RhCE and Kell antigens. Alloimmunization was compared between patients who received extended matched units and those who did not. It was concluded that those who received non-extended matched units were at higher risk to develop alloantibodies (Sins et al., 2016).

In the African content 365 Tanzanian SCD patients were tested for the presence of alloantibodies. 4.1% of these patients tested positive for alloantibodies. Majority of alloantibodies belonged to the kell system (26.2%), Rh system (18%), and Lewis system (18%), MNS system (9.8%) and Colton system (8.2%). More than half of the patients had multiple antibodies(Meda et al., 2014). In neighboring Uganda, a study on 428 SCD patients demonstrated that 6.1% of these patients developed alloantibodies. Majority of alloantibodies belonged to the Rh system (66.7%) and MNS system (16.6%)(Natukunda, Schonewille, Ndugwa, & Brand, 2010).

Similar to the case of alloimmunization in adults, the available literature does not contain enough information on the prevalence of alloimmunization in pediatrics with hemoglobinopathies and multiple transfusions patients. A French study on 175 SCD pediatric patients demonstrated a 7.4% prevalence of alloimmunization amoung these children. The study also suggest that increase in number of RBC units received and presence of preexisting autoantibodies increases risk of alloimmunization. (Allali et al., 2017). Another study in the US demonstrated that multi-transfused pediatric patients who were HLA alloimmunized were more likely to develop RBC alloantibodies(McPherson et al., 2010).

It Is worth to mention that the CDC funded a study on 90 patients to determine the effect of minor antigens and alloimmunization on patients with SCD. The patients were given matched blood for the most common antigens. The study concluded that the presence of preexisting alloantibodies increased the risk for the development of more alloantibodies(Yee et al., 2017).

Prevalence of alloantibodies in thalassemic patients worldwide

Starting with the country harboring the largest population in the world, 382 Chinese patients suffering from thalassemia major were tested for alloantibodies. Of these patients 18.3% developed alloantibodies and the majority had single antibodies detected. Anti-E (39.3%), anti-Mia/Mur (30.85%), and anti-c (13.1%) were the most common detected alloantibodies. Only one patient developed anti-K and 2 developed anti-Fyb antibodies(Cheng, Lee, & Lin, 2012). Moving to the country with the second largest

population, 319 multi-transfused Indian thalassemia patients were tested for alloantibodies. 5.64% of these patients tested positive for the presence of alloantibodies, majority of which were directed against Rh system (52.17%) followed by Kell (35%), Kidd (9%) and Xg (4%) blood systems. This study also found that patients with thalassemia intermedia were more likely to develop alloantibodies(Dhawan et al., 2014). In Eastern India 500 multi-transfused thalassemia patients were screened for alloantibodies. A prevalence of 5.6% of alloimmunization was determined. 52.17% of total alloantibodies found belonged to the Rh system followed by alloantibodies against antigens form the Kidd system(Datta, Mukherjee, Talukder, Bhattacharya, & Mukherjee, 2015).

The Mediterranean is known for its high prevalence of thalassemia patients. A study was carried on 118 Albanian thalassemia patients who were transfused with ABO, Rh and Kell matched blood units for five years. 10.1% of these patients had alloantibodies before the beginning of the study. Most common alloantibodies belonged to the Rh system followed by the Kell blood group. After five years, only 1.7% patients developed alloantibodies (one anti-Cw and one anti-Jkb). The outcome of this study supported evidence that giving extended matched RBC units greatly reduces the risk of the development of alloantibodies (Seferi et al., 2015).

The high prevalence of thalassemia in the African continent emphasis the need for more data to be collected on the incidence of alloimmunization among African patients. In a study carried on 130 Tunisian thalassemia patients to determine the alloimmunization rate, 7.7% of the patients were found to have alloantibodies. Most of these alloantibodies were directed against Rh system followed by anti-Kell and anti-S (Guirat-Dhouib et al., 2011).

697 American thalassemia patients undergoing transfusion therapy were tested for alloantibody production. 16.5% of the patients developed alloantibodies, most of which were directed against Rh antigens follows by anti-Kidd, anti-Kell, anti-Lewis, anti-MNS and anti-Duffy. Half of the patients had multiple alloantibodies. After being age adjusted, alloimmunization rate was not affected by race or gender(Thompson et al., 2011). 64 patients with thalassemia were tested for alloantibodies. 48 (75%) of these patients were from an Asian descendant. 14 (22%) of the patients developed autoantibodies, from which 10 (15.6%) were Asian descendants. In the Asian population 4.8% of the patients developed alloantibodies. Although these patients are residents of the US, they are of Asian descendant, which indicates that they have different phenotypes. Most of the blood donors are whites, and this lead to the increased rate of alloimmunization amoung Asian descendants (Singer et al., 2000). Generally, the alloimmunization in the United States is considerably more prevalent than other areas of the world (except China). This could be attributed to the fact that the United States has a more diverse population compared to other areas of the world. This results in the reduction of the likelihood of random matching between donors and recipient beyond ABO and Rh.

First Author	Country	Disease	Frequency of alloimmunization	Most common antibodies

Natukunda (Natukunda et al., 2010)	Uganda	Sickle Cell Anemia	6.1%	33.3% anti-E 23.3% anti-D 13.3% anti-S
Meda (Meda et al., 2014)	Tanzania	Sickle Cell Anemia	4.1%	19.6% anti-K 14.8% anti-Lea 8.2% anti-Cob
Cheng (Cheng et al., 2012)	China	Thalassemia	18.3%	39.3% anti-E 30.85 anti-Mia/Mur 13.1% anti-c
Datta (Datta et al., 2015)	Eastern India	Thalassemia	5.6%	28.57% anti-c 21.42% anti-E 7.14% anti-Jkb
Dhawan (Dhawan et al., 2014)	India	Thalassemia	5.64%	35% anti-K 17% anti-E 13% anti-D and anti-C
Seferi (Seferi et al., 2015)	Albania	Thalassemia	11.8%	23.9% anti-K 19.1% anti-D 14.3% anti-C and anti-E
Singer (Singer et al., 2000)	USA (Asians)	Thalassemia	20.8%	8.3% anti-K 2.1% anti-E 2.1% anti-c
(Thompson et al., 2011)	USA	Thalassemia	16.5%	19.0% anti-E 18.1% anti-K 9.5% anti-C
Guirat-Dhouib (Guirat-Dhouib et al., 2011)	Tunisia	Thalassemia	7.7%	40% anti-E and anti-C 20% anti-D 10% anti-K

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