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# Detection of presensitization in recipients of kidney transplants

**Research Article**

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**Abstract:** Objective. The preformed antibodies detection in potential kidney recipients is necessary in pretransplant evaluation. The aim of this study was to determine the correlation between the application of blood transfusions and sensitization level in potential kidney transplants. Methods. The study included 268 potential kidney transplants from the region of Vojvodina. The presence of preformed antibodies was tested by microlymphocitotoxicity test. Pearson's correlation coefficient was applied to determine the influence of three variables on sensitization level: number and volume of transfused blood units and time elapsed from last transfused unit. Results. Of 268 eligible patients, 206 patients had a history of blood transfusion. Results of the study showed that the application of great number and volume of transfused units increased the sensitization level (correlation coefficients were r = +0,283 and r = +0,235, respectively) with statistical significance as well as the negative correlation between the time elapsed from the last transfusion and the degree of sensitization (r = -0,082) with no statistical significance. Conclusion. Our study revealed that there is a stronger positive correlation between the number of received blood units than the volume of received blood products and the level of preformed antibodies.

**Keywords:** *Anti-HLA antibodies • Preformed antibodies • Kidney transplantation • Sensitization*



## 1. Introduction

Surgical procedure of kidney transplantation has completely changed the treatment and the outcome of patients in the final stage of kidney insufficiency, offering by far the most cost beneficial treatment in comparison to all so far used procedures. Despite that, the complications such as acute and chronic graft rejection and immunosuppressive therapy side effects are not yet fully overcome. The progress and development in the field of immunology and successful management of transplantation programs have led to an increase in the graft survival rate in the previous decade, despite the fact that both recipients and donors' age are increasing, e.g. from 1990 until 2004 the median age increased from 43 to 51 [1]. According to the UCLA immunogenetics center research data, during the period from 1999 until 2003, five year graft survival rates and projected ten years long graft survival were 80.5% and 67% respectively after a living donor organ transplantation and 68.8% for a five year long survival and 50.9% for projected ten years long graft survival after a deceased donor kidney transplantation [2,3]. Improved desensitization protocols and paired kidney exchange programs provide higher rate of successful transplantation for patients who were previously "untransplantable", having high titers of donor-specific human leukocyte antigen antibodies [4]. Transplant candidates are ranked on the waiting list by using different objective medical and patient-oriented criteria: HLA-A, B, DR match (the so-termed "mismatch probability", age, medical urgency, time period spent on the waiting list, the degree of the previous sensitization of the recipient and distance factor [5,6]. It has been proved that blood

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transfusion, pregnancy and previous transplantation lead to alloimmunization to human leukocyte antigens (HLA), which represents a significant issue in determining the renal transplantation candidates [7-9]. Preformed anti-HLA antibodies can cause a positive cross match with a certain donor as well as the need for the usage of more potent immunosuppressive therapy in order to prevent an acute graft rejection and to improve the allograft life span. Numerous studies have shown the correlation between the number of received blood units and the duration of transfusion therapy with the level of patient sensitization [10-15]. The aim of this study is to determine the degree of sensitization in patients awaiting renal transplantation and to determine the effect of number and type of blood units, as well as the time elapsed from the last application of blood products, to the degree of sensitization.

## 2. Materials and methods

Data on 268 patients (127 male, 79 female) on a kidney transplant program (living or cadaveric transplants candidates) from the region of Vojvodina, Serbia, with a median age of 46.39 who were evaluated for the presence of cytotoxic antibodies before kidney transplantation was included in this study. An informed consent of the individuals participating in the study was obtained and all institutional ethics requirements were met. Data containing the number of received blood units as well as the date of the last transfusion recipience in investigated group of patients were analyzed retrospectively. The most recent serum of every patient was obtained and screened for the presence of preformed anti-HLA I class antibodies by using the complement dependent cytotoxicity (CDC) test (NIH – National Institute of Health technique) according to Terasaki. Each patient's serum was screened by using a whole lymphocyte population consisting of a panel of 20 cells obtained from different randomly chosen HLA(Human Leukocyte Antigens) -A, -B and -DRB1 typed donors covering all alleles detected in the population of Vojvodina. In essence, recipients' sera (1 μL) were dispensed onto Terasaki trays and positive and negative controls were included for the purpose of quality control. The negative control comprised of sera from untransfused male AB blood group donors. The positive controls were pooled sera obtained from patients with a PRA% (Panel Reactive Antibodies) greater than 80%. Fresh donor cells (1 μL of a 2 x 106/mL suspension) in Hanks solution (Bio-Rad, Germany) were added and incubated at room temperature for 30 minutes. Following this incubation, 5 μL of rabbit complement was added to each well, and tray incubated for 60 minutes at 220C. The lysed and vital lymphocytes were assessed using 5 μL of 5% eosin dye (Merck, Germany) and subsequent addition of 6 μL of 37% formaldehyde (Sigma-Aldrich) under an inverse phase contrast microscope [16]. Reactivity against 10% or more of the screening panel members indicated significant presensitization (preformed antibodies).

### 2.1 Statistical methods

All statistical analyses were performed with the software Microsoft Office Excel 2007 for Windows. We investigated the correlation between the degree of sensitization and three variables: the number of transfused blood units, the amount of received blood products in milliliters and the length of time that has elapsed since the last transfused blood product unit, by using Pearson's correlation coefficient and its statistical significance. The impact of the received blood product type (filtered and unfiltered blood) on the sensitization degree was investigated by testing the significance of the difference in average sensitivity between the two groups of patients, using t-test and calculating the difference between arithmetic means compared to the standard error. The *Pearson's chi-squared test* ($\chi^2$) was used for showing the difference between sensitization levels in patients without history of receiving blood units vs. patients who previously have received blood units [17].

## 3. Results

62 (23.13%), (44 males and 18 females) out of 268 eligible patients on kidney transplant waiting list have no history of receiving blood units. Consequently, our studied group included the 206 patients (76.87%) with a history of received blood units before transplantation. The average level of sensitization for the group of patients who did not receive blood units was 7.66% while the average level of sensitization obtained for the group that received blood units was 16.04%, with a statistical difference in number of sensitized patients ($\chi^2$ =5.24, border value is 3.841, $p<0.05$). The average number of previous pregnancies in the females studied was 1.4676. The distribution of patients across the groups formed according to the type of received blood product with an average level of sensitization for each group can be viewed in Table 1.

The degree of sensitization and the number of transfused blood units with consideration of the duration of time elapsed from the last received transfusion is given in Figure 1.

**Table 1.** Average sensitization in potential recipients of kidney transplants.

**Average level of sensitization with an average number and amount of received blood products and time elapsed from last transfusion**

*OAS = Optimal Additive Solution*

| Type of received blood units | Number of patients | Average level of sensitization (%) | Average number of transfused blood units | Average amount of received blood products in milliliters | Average number of months elapsed from the last transfused blood unit |
|---|---|---|---|---|---|
| Patients who received red blood cell concentrates, red blood cells in OAS and filtered red blood cells | 45 | 23,78 | 57,89 | 18059 | 23,24 |
| Patients who received red blood cell concentrates and red blood cells in OAS | 124 | 15,16 | 18,33 | 5597 | 22,06 |
| Patients who received red blood cell concentrates and filtered red blood cells | 3 | 0 | 9 | 2569 | 17,33 |
| Patients who received red blood cells in OAS and filtered red blood cells | 1 | 0 | 7 | 2580 | 0 |
| Patients who received only red blood cell concentrates | 26 | 11,54 | 2,42 | 567 | 20,77 |
| Patients who received only red blood cells in OAS | 5 | 6 | 3 | 1141 | 35,4 |
| Patients who received only filtered red blood cells | 2 | 12,5 | 2 | 769 | 19 |
| total | 206 | 16,04 | 24,24 | 7471,03 | 22,28 |

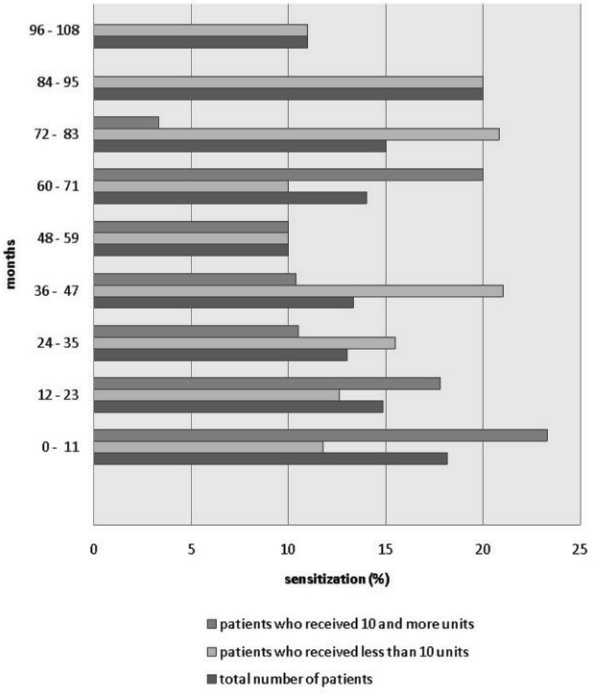


**Figure 1.** Codependence of the level of sensitization and the time elapsed from the last received transfusion until the moment of testing taking simultaneously into consideration the number of received units.
Months – months elapsed from the last transfused blood product until the moment of testing.
Sensitization (%) - average level of sensitization expressed in percentages

The highest number of patients – 101 (49.03%) received less than 10 blood units with an average level of sensitization of 13.61%, while the average levels of patient's sensitivity starting from the group of patients who received 1 to 9 units and ending with the group that received 130 to 135 units, were 13.61%, 13.46%, 12%, 13%, 30%, 7.85%, 27.86%, 17.5%, 32.5%, 52.5%, 18.75%, 0%, 27%, 46.25% respectively.

The degree of sensitization and the amount of received blood products in milliliters taking into consideration the time elapsed from the last transfusion is given in Figure 2.

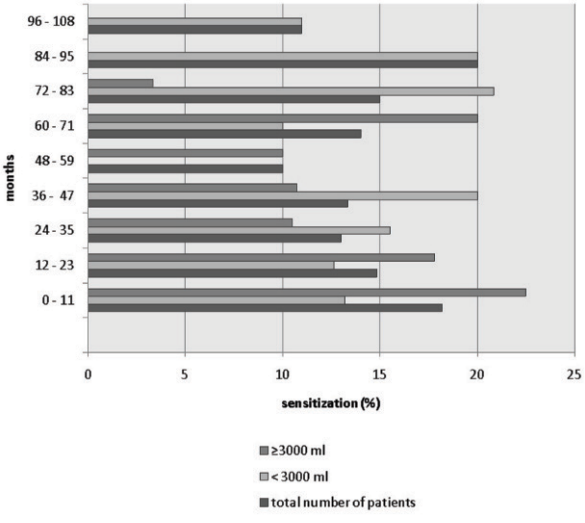


**Figure 2.** Codependence of the level of sensitization and the time elapsed from the last received transfusion taking into consideration volume of received units.
< 3000 mL - patients who received less than 3000 mL of blood products
≥ 3000 mL - patients who received 3000 mL and more of blood products.
Months - months elapsed from the last transfused blood product until the moment of testing.
Sensitization (%) - average level of sensitization expressed in percentages.

An average amount of blood products that patients received was 7471 mL. Two groups of patients have been formed: group of 102 (49.51%) patients who received less than 3000 mL of blood products with an average sensitization level of 14.22%, and the group of 104 (50.49%) of patients who received 3000 and more milliliters of blood transfusion units with an average sensitization level of 17.84%.

The level of sensitization and the time elapsed from the last transfused blood unit taking into consideration the type of received blood units is given in Figure 3.

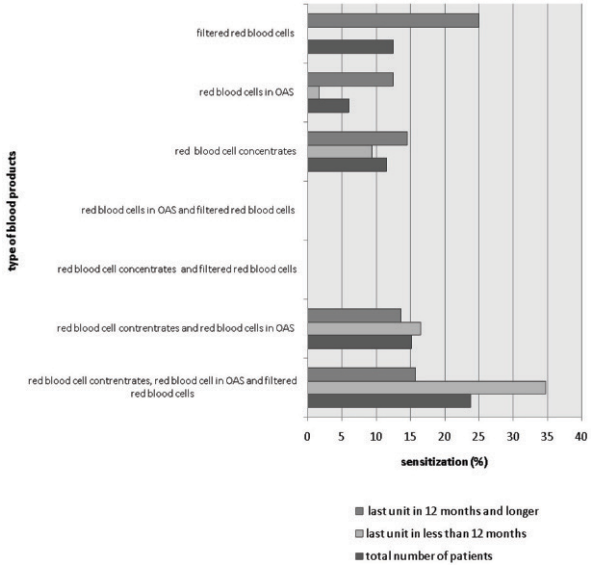


**Figure 3.** Correlation between the average level of sensitization and type of received blood units considering time period from last received unit until moment of testing. OAS-Optimal Additive Solution.

The time elapsed from the last received transfusion until the moment of testing varied in wide range, from 0 until 108 months and analysis showed that the longer the period from the last received transfusion was, the lower were the values of the average sensitization. Therefore, the group of patients who received the last transfusion within one year until the moment of testing showed the average value of sensitivity level of 18.17%, the group of patients who received last transfusion in period less than one month before the moment of testing showed higher average sensitization level of 20.36% opposed to the group with longer period of time elapsed (96 to 108 months) with 11% of average sensitization.

For analyzing the correlation between the degree of sensitization and three variables, the number of transfused blood units, the amount of received blood products in milliliters and the period of time elapsed since the last transfused blood product, the Pearson's correlation coefficients - r and its statistical significance – t were used (Table 2).

**Table 2.** Correlation coefficient between degree of sensitization and presented variables.

| Correlation coefficient and its statistical significance | | | |
|---|---|---|---|
| | Correlation coefficient r | Statistical significance t | Confirmed statistical significance P<0.05, border value t= 1.94 |
| Number of received blood units | + 0.283 | 4.2305 | yes |
| Volume of received units | + 0.235 | 3.453 | yes |
| Time elapsed since the last transfused blood product | - 0.082 | 1.175 | no |

The presence of a positive correlation between the number of received blood product units and the level of patient's sensitization has been proved, since the correlation coefficient was r = +0.283 and the result of its statistical significance t = 4.2305 with the degree of freedom V=204 and border value for p<0.05, t= 1.94.

The positive correlation between the volume of blood products that each patient had received and the sensitization level was proved by obtaining the correlation coefficient of r = +0.235, with its statistical significance t = 3.453, with the degree of freedom V=204 and border value for p<0.05, t= 1.94.

The negative correlation between the time elapsed from the date of the last received transfusion until the moment of testing and the level of patient's sensitization has been proved, since the by correlation coefficient was r = -0.082 with no statistical significance: t =1.175, with the degree of freedom V=204 and border value for p<0.05, t= 1.97.

For determination of the impact of the received blood product type (filtered and unfiltered blood) on the sensitization degree, patients were divided in two groups: group of 51 patients(24.76%) who received filtered red blood cells units with an average value of sensitization of 21.47% and 155 patients (75.24%) who did not receive filtered red blood cells units, for whom an average level of sensitization was 14.26%. The impact of filtered blood products on the sensitization level was investigated by testing the significance of the difference in average sensitivity between the two groups, using t-test. The obtained result with t= -0.797, the degree of freedom V=204, border value for p<0.05, t= 1.97, showed no statistical significance in the difference between the average sensitization levels in two investigated groups.

## 4. Discussion

Previous sensitization in the patients awaiting the organ transplantation represents the presence of previously formed anti HLA antibodies (immunoglobulins class IgM or IgG), formed after foreign HLA antigens contact accomplished by blood transfusions, previous transplantation and pregnancy, microorganisms, ingested proteins, allergens, or foreign objects [18]. Presensitization plays a significant role in management of potential kidney transplant recipients since a significant proportion of patients with end stage renal disease often does not reach full potential benefits of transplantation as a result of allosensitization. It is certainly useful criteria for planning the post-transplantation immunosuppressive therapy considering the higher occurrence of acute transplant rejections, delayed graft function and the decrease of long-term graft survival rate in this group of patients [13,19,20]. Also, the increased waiting time period on transplantation waiting lists thus increasing mortality rate can also be expected in patients with prior sensitization. Broadly sensitized patients in average spend almost more than twice as long on a kidney transplant list as unsensitized patients do [21-24].

Periodical controlling of presensitization level is compulsory with kidney transplant candidates due to its variation over time. In our transplant center, we usually test the presence of anti- HLA antibodies every three months using various techniques with the minimum sensitivity equal to CDC technique which is applied in this study. Approximate number of patients awaiting kidney transplants in the center where the study was conducted is around 180. Our main goal was to show the influence of received blood products on the level of preformed anti-HLA antibodies in potential renal graft recipients. The results of our study are in accordance with numerous studies that have shown increased risk of HLA antibody development in patients with history of transfusions compared to the patients who did not have any transfusions. (16.04% vs 7.66%, with a statistical difference in number of sensitizated patients ($\chi^2$=5.24). Balasubramaniam GS. et al., [13] demonstrated a statistical significance by chi-square analysis in the association between blood transfusion and HLA antibodies positive patients. Vaidya S. [14] analyzed a cohort of 425 patients which showed that patients immunized by prior transfusions and/or pregnancies synthesized broad reactive HLA antibodies following either acute or chronic rejection (p=0.0009 and 0.001, respectively). In the study conducted by Eikmans M. et al., [10] researchers found that blood transfusion in both nonsensitized recipients and sensitized recipients lead to activation of the recipient's immune system. They also showed that in previously sensitized recipients HLA antibody formation occurred more often, in contrast to the nonsensitized recipients. Scornik et al., [15] demonstrated that previous pregnancies and transplantations were major risk factors for broad immunization after blood transfusion.

We also confirmed the direct influence of number and volume of received transfusion units on the level of prior sensitization by obtaining positive correlation coefficient values between these variables (r=+0.283 and +0.235) which were both statistically significant (t = 4.2305 and t = 3.453 respectively). Number of the received blood units and the level of sensitization showed stronger positive correlation with a higher value of correlation coefficient in comparison to the volume of received blood as a variable. That could be explained by the fact that among all used blood products, red blood cells in OAS represent 36.18% and they contain additional volume of optimal additive solution leaking blood cells which does not enhance sensitization.

Despite the expectation that the sensitization rates will be lower in potential recipients who are transfused with leukoreduced blood products, some studies show no difference in risk of allosensitization between the patients who received blood product with no leukocyte reduction and those who received leukodepleted blood transfusion. In the 1980s, SanFilippo et al. [25] conducted a randomized study transfusing renal transplant candidates with either standard or leukoreduced red blood cell units and found no difference in allosensitization rate. According to study of Karpinski et al., [26] no significant difference in the rate of transfusion-associated allosensitization in renal transplant candidates who received either standard or leukoreduced red blood cell transfusions were found (27% versus 33%, respectively). According to Vamvakas, [27] despite the reduction of leukocytes in the received blood products, the rates of alloimmunization in different studies vary considerably and range from 7% to 44% among recipients of leukocyte-reduced blood transfusions and from 20% to 50% among control recipients of non-leukoreduced blood components. Results of our study are in accordance with the results mentioned above, since we demonstrated no statistically significant difference in the average levels of sensitization for both the group of patients who received filtrated blood products and the group of patients who received standard blood products (t= -0.797, border value for p<0.05, t= 1.97). Our results could be explained by the fact that among the group of patients who received leukodepleted blood products, females, who have relatively higher chance to be alloimmunized than males due to previous pregnancies, represent 25.94% of group, which is higher than 17.06% of women

in the group of patients who received non leukodepleted blood products. Another explanation for the fact that our study showed no statistically significant difference in the average levels of sensitization for the group of patients who received filtrated blood products vs. the group of patients who received standard blood products was the fact that both leukocytes and red cells carry a significant HLA antigen load, and residual leukocytes and/or red cell HLA may explain why leukocyte-reduced units are unable to prevent sensitization to any significant degree [28,29]. Evaluation of the influence of time elapsed from the last transfusion on the sensitization level confirmed expected (negative) correlation - the longer the period from the last transfusion received the lower values of the average sensitization were shown. Decline in levels of formed antibodies over time as well as recovery of recipient's immune system after a sensitizing event is not certain, because antibody levels rise and decline over time depending on numerous individual parameters and sensitivity of tests used for the antibody detection.

The limitation of this study, in our opinion, is the fact that we did not manage to form large enough, uniform groups regarding the type of received blood products containing exclusively one blood product type. One reason is that the use of filtered blood products in our transplant center is disproportionately small compared to the need, due to the lack of pre or/and post storage leukodepletion filters for whole blood donations. Also, in our study out of 268 patients, 206 (76.87%) patients received pre-transplant blood transfusions, and the an explanation for this high proportion of blood transfusion usage is that there is lack of highly recommended erythropoiesis-stimulating agents in our transplant center.

Increasing the risk of allosensitization in patients awaiting kidney transplantation should always be avoided considering significant share of these patients in total potential kidney transplant recipients. According to Marfo K. et al. [30] 35% of the patients on the waiting list are currently sensitized with panel reactive antibody (PRA) levels >0%, and 15% are highly sensitized with PRA levels >80. Based on the data given by Peng A. et al., [8] in 2003, 32% of the patients on the transplant list were considered sensitized to HLA antigens and 13.7% had sensitization level greater than 80%. However, in some situations clinical need for a blood transfusion outweighs the risk of sensitization, so appropriate patient therapy protocols must be provided with regards to the risk of allosensitization after leukodepleted as well as standard blood transfusions. Additionally, resolution of the allosensitization problem can be obtained through: a brief course of immunosuppression beginning at the time of transfusion, usage of HLA matched transfusions and introduction of less allogenic blood substitutes or modified blood products in the future [26]. In conclusion, in the group of patients awaiting kidney transplants who received transfusions, the positive correlation between the number of received blood units and the level of preformed antibodies was determined. The negative correlation between the time elapsed from the date of last transfusion and the sensitization level in these patients was determined. Considering the influence of blood product usage to the level of previous sensitization, more rational usage of blood products in renal patient therapy protocols can influence the decrease of the sensitization level of these patients before transplantation.

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