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Review

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Immunologic Risk Assessment before Kidney Transplantation: An Update

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Abstract

The most important kidney transplantation antigens are the ABO blood group antigens and the products of the major histocompatibility complex (MHC). The MHC antigens are called human leukocyte antigens (HLA). Exposure to foreign HLA through previous transplantations, blood transfusions and pregnancies are the most important risk factors for the development of anti-HLA antibodies. Along with improvements over the past 50 years in the detection of anti-HLA antibodies, one of the most important advances in facilitating transplantation of sensitized patients has been the ability to accurately characterize anti-HLA antibodies specificity using solid phase immunoassays. Cross-match testing with cytotoxic analysis has long been supplemented by flow cytometry, but development of solid-phase single antigen bead testing of solubilized HLA to detect donor-specific HLA antibodies (DSA) permits a far more nuanced stratification of immunological risk status, including the different classes and intensities of HLA antibodies class I and/or II, including HLA-DSA. Immunologic risk evaluation is now often based on a combination of all of these tests. In this process, the most important assistant of the clinician is an effective communication with the immunology team and the planning immunosuppressive treatment regimen should be decided according to pre-transplant immunologic risk levels.

Keywords: Kidney transplantation, immunologic risk, donor specific HLA antibodies, sensitization

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INTRODUCTION

Kidney transplantation is an effective replacement therapy for the majority of patients with end-stage kidney disease (1). A successful kidney transplantation provides higher survival and better quality of life than chronic dialysis treatment (2). Risk assessment before kidney transplantation may include many factors, but there is no clear consensus on which parameters to consider and their relative importance. One of the most important aspects of the pre-transplant evaluation is the evaluation of the immunological compatibility between the recipient candidate and potential donor or cadaveric donor. The most important objective of this evaluation is to differentiate between a high immunological risk recipient, such as those with a history of recurrent transplants, blood transfusions, pregnancy, or organ transplants, and a standard immunological risk recipient, such as those with no history of first transplantation, blood transfusion, pregnancy, or organ transplantation. In this way, the clinician decides to plan the most appropriate immunosuppressive treatment regimen in the management of these patients (3). During this process, the clinician's most important helpers are the immunology team with a well-equipped human leukocyte antigen (HLA) laboratory.

The pre-transplant immunological risk assessment can be collected under four main headings:

I. Assessing the compatibility of ABO
II. Evaluating the HLA compatibility
III. Testing the presence of anti-HLA antibodies
IV. Cross-matching (XM) tests.

The results of these four parameters should be interpreted together with the previous transplantations of the patient and histories of pregnancy and blood transfusion, and an immunological risk assessment should be calculated accordingly during the evaluation of the immunological compatibility between each recipient candidate and the living or cadaveric donor.

I. Blood group compatibility: One of the conditions that should be evaluated first under our country conditions is the ABO compatibility between the recipient and the potential donor.

As known, with the anti-HLA antibodies being tested in the 1960s using the XM test, one of the most important obstacles in kidney transplantation has been the ABO blood group barrier and therefore isoagglutinins (4). The ABO blood group system was discovered by Karl Landsteiner, an Austrian physician, at the beginning of the 20th century. The ABO blood group system consists of four main groups: A, B, AB, and O, and the most common ones in the US population are the A and O blood groups (Table 1) (5). Similarly, in the evaluation of blood group screening with the largest population in our country, the A and O blood groups were most frequently determined (6). The ABO blood group system is not only involved in blood transfusion. ABO blood group antigens are not only found in erythrocytes but also found in lymphocytes, platelets, and epithelial and endothelial cells; thus, they play a more effective role in kidney transplantation than the HLA antigen system. Rh factor and other erythrocyte antigens are not as important as ABO compatibility since they do not exist in the endothelium. The formation of blood group antibodies occurs against antigens that are not specific to the host. According to Landsteiner's theory, both A and B antibodies are found in an individual with blood type O, whereas there is no antibody against A or B antigens in an individual with an AB type blood group. Considering the distribution of blood group antigens in the US, it is reported that the waiting period for patients with the B and O blood groups is significantly prolonged. In addition, individuals with the O blood group tend to have higher isoagglutinin antibody titers than those with both A and B antigens (5, 7).

The A blood group consists of two subgroups: A1 and A2. Approximately 80% of the individuals with the A blood group present with A1. The antigenic property of A2 is less than that of A1, and the overall immunological risk based on antigen presentation is A1>B>A2 (8).

Considering the low immunological risk of the A2 antigen, in some countries, the disadvantage of individuals with the O and B blood groups with respect to the waiting time brought the idea of kidney transplantation from A2 donors (9). The first successful ABO incompatible kidney transplantation was reported in Belgium in 1985 with desensitization and immunosuppression (10). Then, in 1989, long-term survival success was reported from Sweden in transplants to the O and B blood groups from the A2 subgroup, which was less antigenic (11). ABO incompatibility is a problem encountered in 10%-30% of the potential donor candidates. ABO incompatible kidney transplantation practices have increased since the late 1980s in Japan, the mid-1990s in the US, and the early 2000s in Europe due to increased donor limitations (9). In the US, the A2 subgroup has been implemented in the Organ Procurement and Transplant Network since 2014, since transplantation to the O and B groups significantly reduced the waiting times for transplantation without significantly increasing the risk of graft loss and/or death (12-14).

The aim of desensitization in ABO incompatible transplantation is to lower and maintain the anti-A/B antibodies (isoagglutinin antibody titer) below a threshold that is considered safe for the first 2 weeks post-transplant (target isoagglutinin titer ≤1/8-1/32). The two main methods used to reduce circulating ABO antibody titers are plasmapheresis and immunoadsorption. Intravenous immunoglobulin (IVIG), splenectomy, and rituximab are used as additional adjunct therapies (9). Although high rates (10%-30%) of acute antibody-mediated rejection (AMR) are observed under today's conditions, long-term graft and patient survival of ABO incompatible kidney transplantation is equal to that of ABO compatible kidney transplantation (15-17).

In recent years, ABO incompatible kidney transplantation has become a routine practice, with an approximately 30% increase in the living donor pool, but when combined with the risk of acute AMR, intensive immunosuppressive necessity and cost suspicions limit the prevalence of ABO incompatible kidney transplantation. ABO incompatible kidney transplant recipients are at increased risk for viral, such as cytomegalovirus, herpes simplex virus, varicella zoster virus, pneumocystis pneumonia, and BK virus, wound, and urinary tract infections compared with ABO compatible kidney transplant recipients. In addition, owing to the loss of clotting factors as a result of the apheresis procedure, it causes a perioperative increased risk of bleeding (9).

In our country, ABO incompatible transplantation cannot be performed since it has been excluded from the refund with the Social Security Institution notification in 2010. Transplantation of A2 to patients with the O and B blood groups is also not permitted. According to the results of the current analysis, cost-effectiveness analysis is not very negative, and ABO incompatible transplantation with these implementations appears to be able to provide an increase in living donor pool in our country. We believe that it is necessary to allow ABO incompatible transplantation in appropriate centers by determining the characteristics and conditions until an effectively functioning national donor exchange program is initiated. In kidney transplantation, blood transfusion rules apply regardless of Rh compatibility. The O group is the general donor, and the AB group is the general recipient. One of the first parameters to be examined during pre-transplant evaluation is whether there is compatibility between the recipient and the donor candidate (Table 1).

Table 1. Recipient blood groups, frequencies in the population, and compatible blood group donors

Recipient blood group	Percent in the population (%)	Donor blood group compatible with recipient
A	42	A, O
B	10	B, O
AB	4	A, B, AB, O
O	44	O

Reference no. 5.

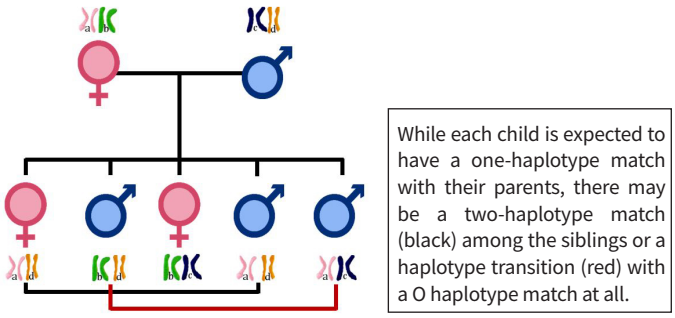

Figure 1. Inheritance model for HLA genes

II. HLA compatibility: The gene region encoding the tissue antigens required for the immune system to recognize the self and non-self is called major histocompatibility complex (MHC). In humans, MHC molecules are called HLA and are another antigen system that should be evaluated before kidney transplantation. These antigens, which were initially identified in leukocytes, have been shown to be present in many immune and non-immune cells in our body. The genes responsible for the synthesis of these antigens are located in a complex in the short arm of the 6th chromosome and function in three parts as classes I, II, and III. Class I and II genes encode HLA molecules that are important in transplantation. Class III genes encode other proteins associated with the immune system, including cytokines, complement factors, and heat shock proteins. The importance of HLA molecules is based on their ability to present peptides to T cells. T cells can recognize peptides in the peptide-binding sites of HLA molecules (18).

HLA class I antigens include HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G. These antigens are found in all nucleated cells and present peptide particles of foreign proteins to CD8 (+) cytotoxic T-lymphocytes. HLA-E, HLA-F, and HLA-G act as binding point for receptors of natural killer cells and have been shown to be important in cytomegalovirus and post-transplant defense. These loci may be important in bone marrow transplantation involving natural killer cells, but their association with solid organ transplantations has not yet been determined. HLA class II antigens include HLA-DR, HLA-DQ, and HLA-DP. These are found on antigen-presenting cells, such as monocytes, macrophages, and dendritic cells, B-lymphocytes, and activated T-lymphocytes and present peptide particles of foreign proteins to CD4 (+) T-lymphocytes (18, 19).

Conventionally, HLA compatibility between recipient and potential donor is assessed on six of these antigens, such as HLA-A, HLA-B, and DR loci. HLA-C, DRB3/4/5, DQA1, DQB1, DPA1, and DPB1 loci are also routinely tested in the US organ distribution system. HLA genes are quite diverse. We all have two haplotypes, one from the mother and the other from the father, so that two forms of the genes (alleles) occur in a single locus. While we can expect a single haplotype compatible with our parents, haplotype transition in siblings may range from full compatible to not compatible at all (20, 21) (Figure 1).

HLA typing is performed in a series of ways to assess HLA compatibility between recipient and potential donor in kidney transplantation and to improve graft and patient survival. The methods used in HLA typing are very advanced in the historical process, starting with serological methods, proceeding to sequence-specific oligonucleotide probes, sequence-specific polymerase chain reaction (PCR), and direct DNA typing. Currently, with the development of PCR technology and the elaboration of HLA genes, HLA typing is performed in many centers using automated or semi-automated sequence-specific oligonucleotide probes (21).

HLA matching remains one of the most important techniques to identify risk factors for kidney transplantation. It is known that for HLA antigens, each mismatch does not have equal weight. It was shown that HLA-A antigens bring less immunological burden than HLA-DR and HLA-B antigens in the Collaborative Transplant Study (CTS) analysis (22). The Eurotransplant and the United Kingdom Transplant Service data similarly showed that HLA-DR matching had better graft survival than HLA-A or HLA-B (23, 24). At the same time, it has been shown that each antigen shows its effect at different times after transplantation; HLA-DR mismatch has the greatest effect in the first 6 months after transplantation, and the greatest effect of HLA-B mismatch occurred in the first 2 years of transplantation (25).

Anti-HLA-DP antibodies are less common than HLA-DR and HLA-DQ antibodies and occur in 5%-14% of the kidney transplant recipients. The frequency of HLA-DP antibodies increases to 45% in retransplanted patients, and it has been reported to have an effect on graft survival, especially in second transplant (26-28). Anti-HLA-DQ antibody formation is seen in 11% of the kidney transplant recipients and increases to 36% after transplantation. The presence of anti-HLA-DQ antibody and HLA-DQ mismatch are associated with increased risk of rejection and reduced graft survival (29, 30). The United Network for Organ Sharing (UNOS) stipulates the typing of HLA-DQ antigens in cadaveric kidney transplants, but does not consider HLA-DQ matching in the algorithms for organ allocation programs (31).

Table 2. Classification of anti-HLA antibody assays

Nomenclature	Assay type	Strengths	Limitations
Cell-based assays	Cytotoxicity	Donor cells are tested directly Widely used	Requires sufficient number of viable cells Not specific for HLA. Low sensitivity. Subjective scoring of test results
	Flow cytometry	Highly sensitivity; multiple parameters are evaluated simultaneously	Requires expensive equipment and expertise
Solid-phase assays		Commercially available kits; very sensitive, high throughput; unaffected by non-HLA antibodies. Can be adapted to test for different immunoglobulin subclasses; semi-automated with objective scoring of reactivity	Amount of target HLA molecule is not always known; contaminating molecules is unknown; increased cost per sample
By method	ELISA	More sensitive than cytotoxicity	High background with some sera; may be inhibited by high IgM levels
	Microbeads based, flow cytometry, Luminex	More sensitive and higher throughput than ELISA; small sample volume requirement; better correlation with the flow cytometry crossmatch	High capital equipment; may be inhibited by high IgM levels
By target	Pooled HLA antigens	High throughput; least expensive of solid phase assays; suitable as an initial screening method	Antigen composition unknown; connot define HLA specificity; may miss antibodies to rare antigens
	HLA phenotypes	Comparable to a cell panel; can provide antibody estimation of specificity and PRA; suitable as an initial screening method	Not suitable for antibody identification in high PRA patients
	Single HLA antigen	Best for identification of antibody specificity in high PRA patients; most sensitive	Interpretation ca be difficult; may miss antibody to rare HLA alleles

The effect of HLA compatibility on 5-year graft survival was found to be 15% before 1995 and 2%-8% after 1995 in a CTS data including the period before 2005 (32). In another CTS data analysis, HLA incompatibility was found to be associated with infection-associated hospitalization and the risk of functional graft death due to more intensive immunosuppressive use and increased rejection therapy. Furthermore, it has been shown that the mismatch in HLA class II antigens has a stronger effect than that in HLA class I (33). Recently, the emphasis on HLA matching has become less important, especially with improved more potent immunosuppressive therapy and better identification of non-immunological factors in transplantation. In addition, the survival benefits of these patients being continued compared with the ones on the waiting list or those remaining in dialysis were another important factors (34). The importance of minimizing HLA mismatch and maximizing matching was emphasized in a recent study analyzing UNOS records from 1983 to 2013. The risk of graft loss with a single number of HLA mismatch was 13%, whereas the risk of graft loss increased to 64% in the case of six HLA mismatches in the evaluation of approximately 190,000 patients in the UNOS database. In addition, in this study, no locus effect was found in contrast to previous studies (35).

As a result, HLA compatibility continues to have a significant effect on graft survival. Graft survival is positively influenced by increased HLA compatibility in cadaveric transplantations, with or without both living and expanded criteria donor, but HLA compatibility is not an absolute requirement today for transplantation. According to the 2016 Turkish Nephrology Society Registry System data, the rates of transplantation with six HLA mismatches are 17% in living transplantations and 1% in cadaveric. It is noteworthy that transplantations are performed predominantly with 2-5 HLA compatibility (36). Addressing the donor with more HLA compatibility as much as possible will be an appropriate approach with respect to future risks in cases where there is more than one potential donor candidate.

Technical advances and nomenclature changes related to HLA typing have also led to difficulties in the evaluation of results. In 2010, the World Health Organization Nomenclature Committee for Factors of the HLA system standardized the nomenclature of the HLA system. According to the current nomenclature, specific HLA gene and HLA allele group as well as specific proteins and DNA variants may also be listed. Today, the first two regions are taken into consideration in solid organ transplantations (20). Considering that technical advances and nomenclature have

reached the final stage in recent years, epitopes of polymorphic amino acid sequences on eplets of HLA antigens have been started to be identified, and anti-HLA antibodies have been reported to be specific to these epitopes, and it has begun to be emphasized that epitope-based matching is superior to antigen matching. It appears that developments in this area need to be actively monitored (37).

III. Anti-HLA antibodies: Sensitization to HLA antigens is an important barrier for both living donor kidney transplant candidates and waitlisted patients. The most important risk factor for the formation of anti-HLA antibodies are previous organ transplantation, blood transfusion and pregnancy. In the US, approximately 25% of the patients on the kidney waiting list are sensitized. A higher sensitization rate is observed in previously transplanted patients, women and African population. On average, as the range of antibody specificity increases in sensitized patients, on waiting time for kidney transplantation is doubled (38). In the UK, 23% of the patients on waiting list are sensitized. Most sensitized patients are female (33% vs. 17%) and mostly patients who are waiting for a kidney transplantation recurrence (52% vs. 15%) (39). The measurement of the presence of anti-HLA antibodies in the recipient candidate is a panel-reactive antibody (PRA) test. Sensitization can be against antigens commonly used in class I and II HLA typing or against non-HLA antigens, such as MHC class I-related chain A, angiotensin II type 1 receptor antibody, and anti-perlecan/LG3 antibodies. Studies in which all of these antibodies have been claimed to be associated with graft survival are available in the literature. AMR due to non-HLA antibodies are rarely reported. Highly sensitization is defined complement-dependent cytotoxicity (CDC)-PRA as ≥80% in the Eurotransplant Study Group and ≥85% in the US (40-42).

One of the most important advance facilitating the transplantation of sensitized patients, with progress in the detection of anti-HLA antibodies over the past 50 years, has been the accurate identification of HLA antibody specificity using the solid-phase immunoassays (SPI). A solid matrix/microparticles that are coated with recombinant HLA class I and II molecules and optical reading method are used in these solid-phase antibody detection assays. A solid microparticle plates coated with soluble HLA antigens are used for the enzyme-linked immunosorbent assay (ELISA) test, and for flow cytometry and Luminex assays microbeads are used. These assays have eliminated many of the problems in cell-based antibody screening because they have identified only HLA-specific antibodies and defined HLA antibodies directed against class II antigens which have previously been difficult to define and are critical for B cell XM interpretations. In addition, these assays have significantly improved the speed of testing and analysis, and allowed screening in the presence of lymphotoxic drugs without the need for viable cells. It also provided a more accurate interpretation of XM results (Table 2). The introduction of the Luminex based single-antigen bead (SAB) technology has enabled the detection of HLA antibodies with sensitized patients, and a more detailed assessment of immunologic risk before kidney transplantation. (43-45).

The use of more sensitive methods has led to an increase in the number of sensitized patients (>80% of the patients with PRA positivity), among both patients in the waiting list and patients who were transplanted or newly added to the list (46). The presence of anti-HLA antibodies leads to longer waiting times on deceased kidney donor waiting lists, the problem of XM positivity with living donor kidney transplantation, and decreasing graft survival with AMR in the early or late stages of the post-transplant period (47-49). According to CTS data, presensitization negatively affects graft survival in the first cadaveric transplantation and retransplanted patients. This negative effect becomes more evident with the increasing number of HLA mismatch (50).

There are centers recommending PRA screening every 3 months in patients on the waiting list. In terms of de novo donor-specific antibody (DSA) development after transplantation, there are also centers recommending PRA follow-up every 3 months in the first 1 year and then annual (51). In our center, PRA screening is applied to the patients on the waiting list every 6 months. As of March 2018, according to the results of 571 patients who were on deceased kidney donor waiting list in Ankara University School of Medicine, Transplantation Center, the results of PRA screening performed by the Luminex method revealed that patients who have negative screening against class I and II antigens are 50%. In addition, 8% of the patients were found to have antibodies against class I antigens, 12% to class II antigens, and 30% to both class I and class II antigens (unpublished data). Sensitization appears to be an important problem for patients on the waiting list in our country.

Anti-HLA antibodies may have different properties with respect to structural and biological behaviors. While the antibodies in the IgG structure are considered to reflect true sensitization to HLA, it is assumed that the antibodies in the IgM structure do not reflect a true anti-HLA sensitization. In studies evaluating subtypes of IgG antibodies (IgG1-4), It has been reported that DSA in the IgG3 type may be associated with acute AMR, whereas antibodies in the IgG4 type may be associated with subclinical AMR. In addition, these antibodies may be produced against T cell (class I antigens) or B cell (predominantly class II antigens). Antibodies that have clinical importance are antibodies that cause complement activation and leads to cytotoxicity. The flow cytometric-XM and the Luminex method can also detect non-cytotoxic (independent of complement activity) and clinically not well-known antibodies. Although positive flow cytometric-XM suggests that it is associated with the risk of rejection and decreased graft survival, it should be examined whether it is DSA and whether it causes complement activity (52-54).

The level of anti-HLA antibodies expressed by the mean fluorescence intensity (MFI) value is a semi-quantitative evaluation

and does not directly indicate the serum level of the antibody, rather indicates the amount of antibody bound to the bead in the test medium. Since the HLA-C, HLA-DQ, and HLA-DP antigens are higher in the test medium, the MFI levels of antibodies against these antigens are higher in the test result. Owing to some technical problems during the Luminex method, the MFI measurement may be incorrectly high or low. Low levels of MFI lead to the underestimation of the antibody in some cases. Despite these problems, currently, MFI levels are now widely used in predicting XM results and in assessing immunological risk. Luminex results should be evaluated together with the patient's history of sensitization, including pregnancies, blood transfusion, and previous kidney transplantation, and the results of cell-based tests (55).

In addition, the ability of these antibodies to activate complement is used for many years as an important criterion for in vivo efficacy. Since 1999, the SAB-C4d, C1q, and C3d methods have been developed that test the complement activating properties of anti-HLA antibodies. The common feature of these assays is that they test whether the in vitro-determined anti-HLA antibody activates different components of the complement pathway. It was suggested that they may be more valuable than MFI values and may give an idea about the in vivo activity of the antibody independent of MFI in the first studies that they were used (56). New developing antibodies that are able to bind C1q in the post-transplant period have been reported to be more related to AMR, and there are also centers that use this test in the routine follow-up after transplantation (57).

IV. XM tests: XM is the test that detects circulating HLA antibody against donor antigens. From the moment a potential donor candidate is definite, cell-based XM tests are the basic tests used to assess immunological compatibility. In these tests, the recipient serum is mixed with donor lymphocytes, the purpose is to test the antibodies that bind to these cells. CDC (NIH-CDC)-XM is the most common method used, is a method used without the addition of anti-human globulin (AHG), and detects the antibodies that activate the complement. The sensitivity is highly influenced by the application technique. A wash step is added to eliminate antibodies that are not clinically relevant in the Amos-modified CDC. AHG is added to strengthen the reaction and to increase the sensitivity in the AHG-modified CDC, thus enabling the detection of antibodies that do not activate the complement. If CDC-XM is positive, the test is repeated by adding dithiothreitol (DTT) and eliminates the reaction resulting from IgM-type antibodies. CDC-positive/DTT-negative test is not a barrier to transplantation. The presence of the CDC-positive/DTT-positive test is indicative of IgG-type antibody and is a contraindication for transplantation unless a desensitization protocol is applied, especially if a DSA is defined. The more sensitive FC-XM test is used to detect antibodies bound to fluorochrome-conjugated AHG cells. It is usually performed routinely in some centers in addition to CDC-XM, but in some centers only performed selectively, such as in cases of retransplantation and in cases of predetermined PRA positivity, due to the risk of sensitization from the child to the mother or from the male partner. The most important disadvantage of these tests is the need for presence of viable lymphocyte, low sensitivity, low specificity for detecting non-HLA antibodies, and varying results even in the same intra-center practices. In today's conditions, non-cytotoxic antibodies as determined by methods such as ELISA, Flow-PRA or Luminex should be considered as a risk factor in transplantation and antibodies detected by CDC should be seen as contraindication (58).

The administration of SPI in kidney transplantation radically changed HLA antibody screening. It allowed for the complete identification of antibody specificities in serum of sensitized patients and monitoring of low-level DSA after transplantation. However, the technical problems in the interpretation of the test results and the large differences in the results revealed the need for standardization. In 2012, the guidelines prepared for screening for HLA antibody in kidney transplantation by the initiative of The Transplantation Society make suggestions on technical problems for the pre-transplant and post-transplant periods (59).

Recommendations of the technical group:

- SPI, especially the SAB assay, must be used for the detection of pretransplant HLA antibodies in solid organ transplant recipients (level 1).
- In addition to SPI, antibody detection should be performed with cell-based assays for prediction of a positive cell-based crossmatch (level 1).
- There must be an awareness of the technical factors influencing antibody testing, such as variation in antigen density, the presence of denatured antigen on the beads, and the prozone effect which can influence the interpretation of test results (level 1).
- History of sensitization, such as previous transplants or transfusions as well as pregnancy in female patients, must be taken into account when interpreting the antibody screening (level 1).
- High resolution HLA typing of donor and recipient must be performed for accurate antibody assessment (level 1).
- Quality control and standardization of laboratory procedures is required to minimize assay variability (level 1).

Pre-transplant group recommendations:

- Risk categories should be established based on antibody and crossmatch results (level 3).
- DSA detected by CDC in the most recent serum must be avoided (level 1).
- Kidney transplantation can be performed in the absence of a prospective crossmatch if highly sensitive single antigen bead screening for antibodies to all class I and II HLA loci is negative (level 3).
- Pretransplant determination of unacceptable HLA antigen mismatches should be part of kidney allocation algorithms (level 2).

- Complete HLA typing is needed for accurate crossmatch prediction. Donor typing should be performed for the HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DQA1, HLA-DQB1, HLA-DPA1, and HLA-DPB1 loci (level 2).
- The presence of DSA is not inevitably a contraindication to transplantation if CDC XM against the donor is negative. The immunologic risk can be lowered by the elimination of DSA desensitization therapy (level 2).
- Highly sensitized recipients should be enrolled in special programs such as kidney paired donation, the Acceptable Mismatch program, or the Heidelberg algorithm in order to increase their chance for receiving a suitable donor organ (level 1).
- HLA matching should be part of the organ allocation algorithms because it prevents sensitization and rejection and increases graft survival (level 2).

Biological approaches, as well as desensitization protocols, can be applied in transplantation in sensitized patients. These protocols can include the removal of anti-HLA antibodies, such as plasmapheresis, immunoadsorption, and IgG-reducing *Streptococcus pyogenes* enzyme, reduction of antibody-producing cells, such as rituximab and bortezomib, suppression of antibody and complementary pathway, such as IVIG, eculizumab, and C1 inhibitor, suppression of inflammation and cytokines, such as IVIG and tocilizumab, and various combinations of these. In some studies, a variety of desensitization programs have been shown to have a survival advantage compared with patients with dialysis. However, despite acceptable short-term recipient and graft survival data, the increase in acute and late AMR has made long-term success of these protocols questionable. Considering the results of desensitization practices, for nephrology experts, evaluating biological approaches of these patients also appears to be a suitable option. It also has advantages, such as kidney paired exchange programs or acceptable mismatch application, administration of less potent immunosuppression, lower acute rejection rates, and better graft survival (60).

CONCLUSION

During the immunological evaluation prior to kidney transplantation, the best possible alignment between the recipient candidate and the potential donor(s), as well as ABO compatibility, should be considered. In addition to being questioned for sensitization risk factors, such as previous transplantations, blood transfusions and pregnancies, the recipient candidate should be evaluated by PRA screening and identified for the evaluation of the status of anti-HLA antibodies. Moreover, in the final stage, immunological risk should be determined by adding the findings of the recipient and donor-specific CDC-XM and if possible, FC-XM results, and the initial and maintenance therapy regimen should be decided according to the level of this risk. Special programs should be implemented for high-risk patients. Centers should identify sensitized patients on the waiting lists and standardize DSA scans-typing and XM applications across the country to develop these special programs. Considering the disadvantages of the desensitization practices such as the cost and the inadequacies of long-term outcomes, “donor exchange programs”, “acceptable missmatch” and “virtual XM” applications may emerge in our country’s conditions. In addition, criteria for kidney distribution scoring should be updated for sensitized patients.

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