

Basic concepts in kidney transplant immunology

Advances in the field of immunohistocompatibility and immunogenetics have been crucial for improvements in kidney transplant outcomes. This review provides a practical outline of these important breakthroughs for the general physician, at a time when demand for kidney transplants is increasing.

Kidney transplant remains the best type of renal replacement therapy in most patients suffering from end-stage kidney disease. Patients can remain on the transplant waiting list for a number of years because of the worldwide shortage of organs. Modern crossmatch techniques and human leukocyte antigen (HLA) typing play a crucial role to ensure better organ allocation and provide the recipient with a more favourable match.

Transplantation of an organ into a genetically different recipient will invariably elicit an immune response because of the presence of alloantigens and allorecognition by the recipient. Foreign major histocompatibility complex (MHC) proteins are recognized by recipient alloreactive T cells via three pathways: direct, indirect and semi-direct (Safinia et al, 2010). In the direct pathway recipient T lymphocytes recognize MHC molecule–peptide complexes on donor antigen-presenting cells. This leads to activation of CD4 helper or CD8 cytotoxic T cells. In the indirect pathway, recipient's antigen-presenting cells present donor peptides to recipient CD4 helper T cells via MHC class II. This also leads to interaction with B-lymphocytes resulting in alloantibody production. The semidirect pathway is a more recently proposed pathway whereby recipient antigen-presenting cells acquire intact donor MHC–peptide complexes via cell-to-cell contact or exosomes and present them to recipient

T cells. Activated allospecific T cells include those with regulatory function and those with effector function. The former attempt to prevent allograft rejection while the latter mediate graft rejection. The proportion of these two T cell populations will ultimately determine the clinical outcome (Afzali et al, 2008). In the absence of immunosuppression these receptor–ligand interactions will inevitably lead to graft rejection. However, despite new and more potent immunosuppressive regimens in the modern transplantation era, the crossmatch still remains an essential tool to identify preformed donor-specific antibodies in recipients who have already been primed to foreign antigens. Allosensitization to HLA proteins occurs after pregnancy, blood transfusion or transplantation.

The importance of performing a crossmatch before renal transplantation was initially demonstrated in the landmark paper by Patel and Terasaki (1969). Since then, a positive complement-dependent cytotoxicity crossmatch (CDC-XM) has generally been considered as a contraindication to transplantation in view of the associated high risk of hyperacute rejection. This type of rejection occurs immediately upon reperfusion and is attributed to preformed donor-specific antibodies to HLA.

Although the CDC-XM is still widely used by many transplant centres, over the years it has mostly been superseded by new crossmatch techniques with higher sensitivity and specificity. These various crossmatch techniques, when performed and interpreted simultaneously, provide invaluable information in the process of successful organ transplant. Another important purpose of tissue crossmatch is as a risk assessment tool for antibody-mediated rejection, which is one of the main barriers to improve long-term graft outcomes (Djamali et al, 2014).

Long-term graft survival is vital since patient outcomes with a functioning allograft are superior to outcomes on dialysis (Tonelli et al, 2011). Moreover, there are medical economic advantages associated with prolonged graft survival (Flechner, 2003). This review discusses the various HLA typing and crossmatch techniques (*Table 1*) and their respective roles in determining transplant decisions towards successful outcomes.

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Table 1. Advantages and disadvantages of crossmatch techniques

Crossmatch technique	Advantages	Disadvantages
CDC-XM	Detection of donor-specific cytotoxic antibodies	Detects immunoglobulin M False positive rate of 20%
Antihuman globulin CDC-XM	Increased sensitivity over the CDC-XM	Detects immunoglobulin M
Flow cytometry crossmatch	Sensitive for low titre antibody Detects non-complement binding antibody	May exclude patients unnecessarily Specificity for human leucocyte antigen antibodies is low May be falsely positive in patients having previously received monoclonal antibodies like rituximab
Virtual crossmatch using single antigen beads	Increased sensitivity May be performed with stored sera therefore shortening cold ischaemia time Improves transplantation access for highly sensitized patients Improves risk assessment for rejection	Denatured human leucocyte antigens on single antigen beads may lead to a false positive result Requires more coordination between immunology lab personnel and transplant team

CDC-XM = complement-dependent cytotoxicity crossmatch.

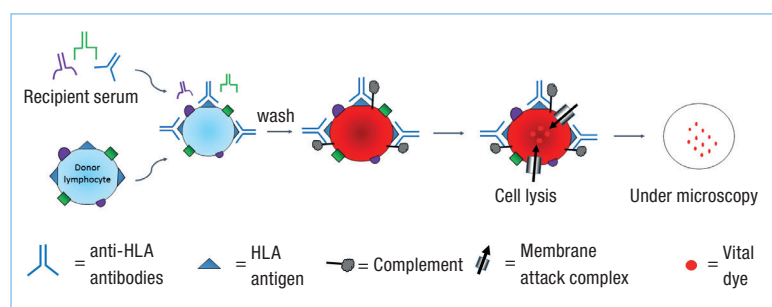
HLA typing

HLA typing and quantification of donor-specific antibodies are prerequisite investigations which facilitate the assessment of the recipient's overall immunological risk. HLA plays a central role in both cellular- and antibody-mediated alloresponses, which determine the outcome of a transplanted organ (Takemoto et al, 2004). For the purpose of kidney transplantation, HLA typing is usually required down to a low or intermediate level of resolution. Automated extraction methods allow for a relatively rapid typing that can be performed in 3–4 hours from the time a sample is received.

Sequence-specific primers and sequence-specific oligonucleotides probes are the most common techniques used for low or intermediate resolution. The sequence-specific primer method uses gene-specific primers followed by amplification (DNA polymerase) and identification by agarose gel electrophoresis. The sequence-specific oligonucleotides probe method uses a gene-specific primer with unique fluorescent tags, which are subsequently identified using a flow cytometer. Sequence-based typing achieves high-level resolution HLA typing (allele level). This type of typing is predominantly useful in bone marrow transplant (Petersdorf et al, 1995), but is increasingly used in the context of live related donations and to fully resolve complex antibody profiles of sensitized potential recipients.

It is well established that a better HLA match is associated with significantly better patient and graft survival (Lim et al, 2012; Opelz and Döhler, 2012). Indeed, HLA mismatches have been significantly associated with death secondary to cardiovascular disease and infection, especially during the first year after transplantation (Opelz and Döhler, 2012). Furthermore HLA-DR mismatches have also been associated with a higher risk of acute rejection, overall graft failure and death-censored graft failure (Lim et al, 2012). When comparing one or two DR mismatches only two HLA-DR mismatches were associated with an increased risk for all the three outcomes above (Lim et al, 2012).

Figure 1. Complement-dependent cytotoxicity crossmatch showing preformed donor-specific antibodies from the recipient's serum binding to human leukocyte antigen (HLA) antigens on the donor lymphocyte. This results in activation of complement, cell lysis and uptake of vital dye.



Lymphocytotoxic crossmatch techniques

Complement-dependent cytotoxicity crossmatch

The CDC-XM is representative of what would happen in vivo. Good quality T- and B-lymphocytes are isolated from the donor's blood and incubated separately with the serum of potential recipients. Rabbit complement is subsequently added and after an appropriate incubation period (which can vary between different methods of CDC-XM), a vital dye (usually eosin) is added together with formalin to fix the cells. Longer incubation periods and additional wash steps, known as the Amos technique, have been introduced to eliminate unbound antibodies before the addition of complement. If donor-specific antibodies are present in recipient serum, these will bind to HLA antigens on donor cells resulting in complement activation via the classical pathway. This ultimately generates the membrane attack complex, which inserts into the lipid bilayer causing cell rupture and uptake of vital dye. These cells are visualized as red (dead) when seen under the microscope (Figure 1).

The result can be scored on a spectrum from two to eight, with two being equivalent to approximately 20% cell lysis and generally indicating a positive result. A score of eight indicates the strongest possible reaction (Bose et al, 2013).

Figure 2. Anti-human globulin complement-dependent cytotoxicity crossmatch enhances the sensitivity of the crossmatch by increasing the number of fragment crystallizable (Fc) receptors for complement binding. HLA = human leukocyte antigen.

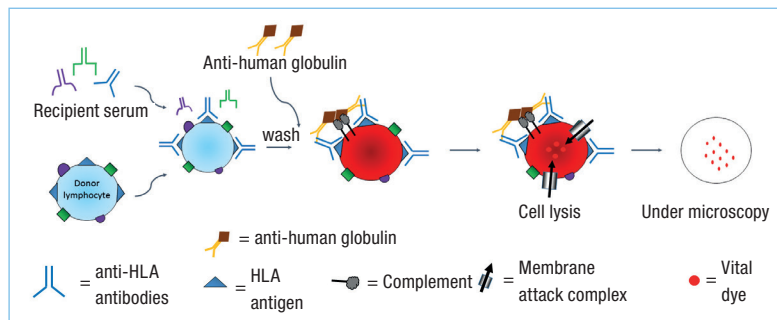
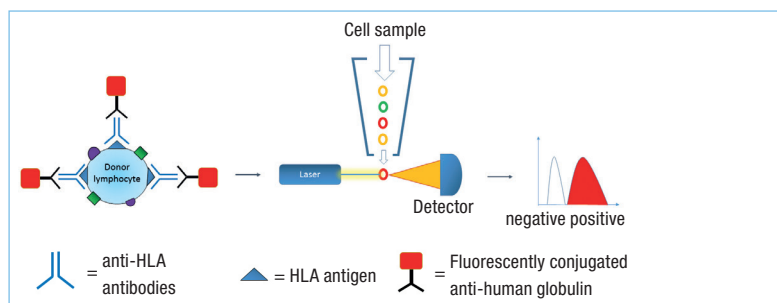


Figure 3. Flow cytometry crossmatch showing fluorescently conjugated anti-human globulin binding to the fragment crystallizable (Fc) portion of anti-human leukocyte antigen (HLA) antibodies, which are bound to HLA antigens on the donor lymphocyte. These are detected and quantified depending on the specific light scatter produced as they pass through the laser interrogation point.



Serial doubling dilutions of the recipient serum is another way to determine the strength of the crossmatch. The more dilutions necessary for the test to become negative, the higher the level of donor-specific antibodies present. Antibodies have to be present in sufficient quantity to link complement to the Fc-receptor and activate complement-mediated cytotoxicity (Gebel and Bray, 2000). The sensitivity of the CDC-XM is enhanced if anti-human globulin is added before the complement factors. This promotes complement fixation by binding to HLA antibody on donor cells and increases the number of Fc-receptors available for complement binding (Figure 2). Low-titre antibodies detected by this method were associated with a 36% 1-year allograft loss compared with 18% loss in those with a negative test (Kerman et al, 1991). The CDC-XM may be applied to both T cells and B cells. The former reflects the presence of HLA class I antibodies, while the latter reflects both HLA class I and II antibodies. Since B cells express higher amounts of class I antigens (Pellegrino et al, 1978), a positive B cell CDC-XM associated with a negative T cell CDC-XM may indicate low levels of class I antibodies.

The CDC-XM has a false positive rate of 20% (Tinckam, 2012). This may arise because of auto-antibodies, which are generally of the IgM and non-HLA IgG type. An auto-crossmatch involves mixing recipient serum with recipient lymphocytes and is usually used to detect these auto-antibodies in question. It is vital to identify a positive

CDC-XM secondary to auto-antibodies, as their presence is not associated with inferior graft outcomes (Bryan et al, 2001). In order to remove the confounding influence of IgM on the crossmatch result, its activity can be eliminated by heating the serum to 55°C since IgM antibodies are cold agglutinins that react best at 4°C. Alternatively, a reducing agent such as dithiothreitol can be added which breaks the disulphide bonds in the IgM pentamer resulting in a negative repeat crossmatch if solitary IgM is present. When interpreting a dithiothreitol crossmatch, it is important to compare to a control group where a diluting agent like phosphate-buffered saline is added, in order to control for the diluting effect that dithiothreitol may have on antibody detection. Consequently if the crossmatch becomes negative with addition of a diluting agent, then the results with dithiothreitol cannot be fully interpreted (Mulley and Kanellis, 2011).

Non-HLA antibodies, which include antibodies against the minor histocompatibility antigens, have also been implicated in acute renal allograft rejection and early graft loss (Tinckam and Chandraker, 2006). There have been reports of a false positive B-cell CDC-XM following treatment with rituximab (Gatault et al, 2013) and basiliximab (Schlaf et al, 2012). One disadvantage of the CDC-XM is that it only detects complement-fixing antibodies, but non-complement fixing antibodies may still be detrimental to graft function (Bose et al, 2013).

Flow cytometry crossmatch

Flow cytometry crossmatch was developed in the 1980s. It served as a more sensitive tool in order to detect donor-specific antibodies that were being missed by the CDC-XM. The technique involves adding recipient serum to donor lymphocytes and then incubating them with fluorescently conjugated anti-human globulin (Figure 3). Additional antibodies with different fluorochromes specific for T-cell and B-cell surface proteins respectively are later added to identify both cell groups. One advantage when compared to the CDC-XM is that it gives a semi-quantitative result, which is therefore less subjective.

The flow cytometer is calibrated using serum from blood group AB unsensitized male donors as a negative control and a pool of sera from highly sensitized patients as a positive control. Electrical impulses generated from the specific forward and side scatter of the laser beam are converted to a numerical value using special software algorithms. The relative median fluorescence of a particular sample is calculated by dividing the median fluorescence of that sample by the median fluorescence of the negative control. The relative median fluorescence is then compared to a predetermined cut-off value. Results from a flow cytometry crossmatch may also be expressed as a median channel shift. A positive control pool is diluted to yield a reasonable shift in fluorescence (displacement between 100 and 300 channels). Usually a cut-off value of two standard deviations is used to define between a positive and negative test. Flow cytometry crossmatch may detect an antibody

subtype according to the fluorescently conjugated anti-human globulin used. Studies have shown a correlation between different IgG classes and adverse transplant outcomes. IgG1 and IgG3, both being complement fixing, are associated with a higher risk (Gao et al, 2014).

False positive results can occur secondary to the binding of non-specific anti-IgG antibodies to immunoglobulin Fc-receptors on B lymphocytes. The enzyme pronase has been used routinely to remove these receptors, improving the sensitivity and specificity of the crossmatch (Lobo et al, 2002). The downside of pronase is that it may reduce HLA expression in a dose-dependent fashion as well as expose cryptic antigens that may be recognized by auto-antibodies, erroneously affecting the final crossmatch result (Park et al, 2012). In addition, the flow cytometry crossmatch may be transiently positive in patients who have received rituximab therapy (Gatault et al, 2013). Flow cytometry crossmatch also detects non-complement binding antibodies. Several studies have suggested that among non-sensitized patients, a positive T or B cell flow cytometry crossmatch does not predict an increased risk for rejection or worse graft survival, whereas inferior graft survival has been reported in sensitized patients (Limaye et al, 2009).

Solid-phase assays

Nowadays the use of solid-phase assays has largely superseded serological methods because of higher sensitivity, specificity and reproducibility. They come in the form of enzyme-linked immunosorbent assays (ELISA) or microbeads. One example is the Luminex technology, which has revolutionized the detection of donor-specific antibodies. Indeed, Luminex single antigen beads (Luminex-SAB) are 10% more sensitive than ELISA, which in turn are 10% more sensitive than serological methods (Gebel and Bray, 2000). For this particular reason most transplant centres use Luminex-SAB even though this technique is more expensive. Analysis of donor-specific antibodies using Luminex-SAB entails the addition of recipient serum potentially containing HLA antibodies to a mixture of synthetic beads each with a unique dye signature (usually red). Each bead is also coated with a specific type of antigen so that anti-HLA antibodies in the potential recipient serum can bind to the corresponding bead. Phycoerythrin-labelled anti-human globulin is subsequently added to the mixture.

The Luminex machine itself is a special type of flow cytometer, which is able to report on 100 different types of simultaneous interrogations (flow is usually able to differentiate about 3–15 different beads or cells at best). Beads are channelled in a single file through the flow chamber where the two laser beams intersect. Each unique bead can then be interrogated for the presence of the reporter dye on its surface and phycoerythrin-labelled anti-human globulin. The light detectors measure the intensities of forward and side scatter, which are converted into electrical impulses. Software will then convert these electrical signals into a meaningful result. Donor-specific

antibodies can be defined according to which kind of cell they interact with (B cell *vs* T cell), current or historic by comparison with stored sera and by their concentration as measured in mean fluorescent intensity.

Luminex-SAB can also be used to identify antibodies directed towards minor histocompatibility antigens. The downside of this technique is the detection of both complement and non-complement binding antibodies and the detection of low level donor-specific antibodies which may refute a potential transplant unnecessarily as it would ultimately result in a negative crossmatch. Another factor to keep in mind when interpreting these assays is the panel of HLA antigens used by the local laboratory. Luminex-SAB may also give false positive results because of denatured antigens on the microbeads (Otten et al, 2013).

The virtual crossmatch

Since the introduction of Luminex-SAB it is now possible to 'virtually' compare specific anti-HLA antibodies in the recipient with the HLA profile of the donor. This is known as the virtual crossmatch. The correlation of the virtual crossmatch with flow cytometry crossmatch is greater than 85% (Bingaman et al, 2008). It requires HLA typing of the donor and a recent anti-HLA profile of the potential recipient. To ensure a correct anti-HLA profile at the time of the transplant call, regular collection of sera every 3 months is required for antibody screening via solid-phase assays, because antibody titres and specificities can change over time. Any potential sensitizing events like pregnancy, blood transfusions and previous transplantation must be documented accurately.

A false negative virtual crossmatch can arise for a number of reasons. Incomplete typing of the donor, as well as donor-specific antibodies in the recipient serum against a unique HLA epitope which is not available on the SAB panel, can give rise to a false negative result (Amico et al, 2009). Of note, not all donor-specific antibodies detected by Luminex-SAB are detrimental to graft outcomes. Studies have shown that donor-specific antibodies detected by SAB but with a negative CDC-XM are a major risk factor for early allograft rejection and long-term graft loss (Mohan et al, 2012). Nonetheless, these are not an absolute contraindication for transplantation if one is prepared to perform desensitization when required, or to use more potent immunosuppressant protocols. False positives may also occur, as mentioned previously, as a result of antibodies directed at HLA epitopes that come about secondary to denatured HLA antigens on the SAB (Otten et al, 2003; El-Awar et al, 2010). Yet another cause for a false positive virtual crossmatch is the presence of null alleles, which are not expressed as antigens on the cell surface *in vivo* (Tinckam, 2012).

One of the principal advantages of performing a virtual crossmatch is the detection of acceptable and unacceptable antigens (Zachary et al, 2008). This avoids unnecessary shipping of organs resulting in less surgery delays, reduces cold ischaemia time, encourages cost savings and improved odds of transplanting highly sensitized patients. A number

KEY POINTS

- Crossmatching before kidney transplantation has evolved immensely with the introduction of the flow cytometry crossmatch and solid phase assays.
- Luminex single antigen bead technology is essential for the detection of donor-specific antibodies both before and after transplant.
- Better HLA match has been associated with superior patient and graft survival.
- The virtual crossmatch ensures timely allocation of organs and increases the chance of transplantation in highly sensitized individuals.
- A potential recipient's immunological history and crossmatch results enable immunological risk stratification before transplantation.

Table 2. Risk stratification for immunological risk pre transplant

Cross match result	Immunological risk
CDC-XM positive and FC-XM negative	High risk
CDC-XM negative and FC-XM positive	Intermediate risk
FC-XM negative and immunoglobulin G class I or II detected by single antigen beads	Standard risk
CDC and/or FC-XM positive and negative Luminex single antigen beads detection	Standard risk
T cell positive, B cell negative CDC and/or FC-XM and positive Luminex single antigen beads but not donor specific	Standard risk

CDC-XM = complement-dependent cytotoxicity crossmatch; FC-XM = flow cytometry crossmatch. Adapted from British Society for Histocompatibility and Immunogenetics/British Transplantation Society (2014)

of studies have reported low risk for early antibody-mediated rejection and good allograft survival even in sensitized patients when using the virtual crossmatch (Bingaman et al, 2008).

The British Society for Histocompatibility and Immunogenetics and British Transplantation Society (2014) *Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies in Allotransplantation* provide recommendations for antibody detection and crossmatching. Furthermore pretransplant immunological risk stratification is discussed based on the crossmatch and current and historic antibody screening results (Table 2) (British Society for Histocompatibility and Immunogenetics and British Transplantation Society, 2014). In potential recipients classified as having an intermediate immunological risk, augmented immunosuppression protocols including induction with antithymocyte globulin or alemtuzumab need to be considered. Although high immunological risk has generally been a contraindication for transplantation, nowadays this risk can be overcome in certain cases by the use of HLA desensitization protocols, including the use of plasma exchange, intravenous gamma globulin and rituximab. In these cases post-transplant surveillance of donor-specific antibodies as well as protocol biopsies, are crucial to facilitate early diagnosis and management of antibody-mediated rejection therefore improving graft survival.

Conclusions

The field of transplant medicine has evolved immensely over the past few years. Despite huge advances in immunosuppression protocols, long-term allograft survival remains an elusive goal. Evidence is attributing poor long-term graft survival to chronic damage secondary to persistent antibody-mediated rejection and transplant glomerulopathy. The development of de novo donor-specific antibodies plays a central role in this process, which is why regular characterization and quantification is of chief importance. Interpretation of these various immunological tools should be performed via a multidisciplinary approach involving transplant physicians, surgeons and immunologists. Integrating these results will ensure an informed decision regarding the viability and safety of proceeding with transplantation. In addition, they provide a means of estimating the recipient immunological risks resulting in patient-tailored immunosuppression protocols and improved outcomes. **BJHM**

Conflict of interest: none.

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