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Sensitization assessment before kidney transplantation

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A B S T R A C T

Kidney transplantation is the treatment of choice for patients with end stage renal disease to optimize survival, freedom from morbidity and quality of life. A fundamental aspect of the pre-transplant assessment is a thorough understanding of their immunological history and prior exposures, so that the immunological risk from a given donor can be estimated, if not quantified, in order to guide interventions to optimize transplant access and success. The methodologies available to complete this assessment have evolved rapidly, with flow cytometric based analyses now standard in many laboratories, availability of comprehensive molecular methods for HLA typing of both donors and recipients, and an increasing recognition of the vital dialogue that must occur between the HLA laboratory and transplant clinicians. This review considers the pre-transplant histocompatibility assessment journey that a recipient undertakes, from initial referral through transplantation, discussing the methodologies used, the benefits and limitations offered by current technologies, and reviewing the basics of interpretation.
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1. Introduction

Renal transplantation is widely acknowledged as the best therapeutic intervention for patients requiring renal replacement therapy. Subsequent graft outcomes are influenced by many patient variables, some of which are modifiable. Acute rejection in the first few months post-transplant is now a relatively rare occurrence but there has been less success in avoiding chronic impairment of graft function in the medium and long-term. Contributing to the reduction in post-transplant acute and chronic rejection is the recognition of the importance of the role of pre-transplant alloimmune sensitization to HLA antigens. An understanding of how sensitization is assessed in the HLA Laboratory is essential for understanding immunologic access to donors of potential recipients as well as peri-transplant decision making, and in communicating to patients these risks and future implications. This review for the general nephrologist will consider the role of HLA laboratory testing in immunologic risk assessment, provide an overview of the methods used in assessing sensitization, and result interpretation and limitations, focusing on HLA antigens and antibodies. Post-transplant antibody monitoring for the development of donor-specific antibody (DSA) and the significance thereof, as well as the roles of non-HLA antibodies are outside the scope of this review.

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2. What is sensitization?

In pre-transplant assessment, sensitization is the detection in the intended recipient of antibodies with reactivity to one or more human leucocyte antigens (HLA). Partly due to their strong relevance in transplant immunobiology, the HLA genes and corresponding proteins (antigens) are well characterized and have been extensively studied, with an ever-increasing number of alleles described [1]. Limited by early testing technologies, HLA A, B and DR antigens and their corresponding antibodies were the most commonly studied. However it is now well recognized that differences at all HLA loci have the potential to result in allorecognition and subsequent alloimmune damage [2,3].

The production of an antibody response requires presentation of an antigen to T and B cells that generates a sufficient signal to promote T and B cell activation. This simple statement demonstrates the two crucial aspects of sensitization – the need for exposure to a relevant antigen, and a (functioning) immune system able to respond to that antigen being presented. Typical sensitizing events include pregnancy, blood transfusion, and prior transplantation. In all scenarios, there is the introduction of non-self-tissue with the potential for non-self-antigen (or part of non-self-antigen) presentation to circulating T and B cells [4]. If sufficiently different to the host, HLA antigen recognition occurs, and in addition to T cell mediated inflammatory pathways, B cell pathways are activated, anti-HLA antibodies may be produced and detected in the peripheral blood. Additionally, memory B cell pathways may be activated such that, if antibodies wane, memory antibody responses may still occur rapidly upon re-stimulation (for example with a transplant that shares similar antigen(s) to the original stimulating exposure). Classically described as hyperacute rejection for over half a century [5], if circulating HLA antibodies are specific to epitopes of antigens present on a graft and present in high enough

titer, immediate recognition will occur with full activation of the immune system, including complement pathways, and destruction of said graft endothelium. However less dramatic, but nonetheless impactful, presentations of antibody mediated damage may occur. Our ability to detect the presence of relevant antibody has necessarily evolved from a coarse co-culture of donor and recipient tissues to highly sensitive flow cytometry based analyses able to detect very low level, but nonetheless potentially pathogenic antibody. With technology advancement, we now recognize that the immediate clinical consequence of all antibody able to be detected is not absolute and clinicians may now be confronted with positive antibody detection in the absence of clinical pathology or dysfunction or even with nonspecific results of unclear significance [6]. Interpretation of risk assessment for patients is now, more than ever, critically dependent on a bidirectional dialogue between clinicians and the histocompatibility laboratory, rather than the simple reporting and receipt of a dichotomous test result.

3. HLA laboratory testing and pre-transplant risk assessment (Fig. 1)

The core immunologic testing platforms to define sensitization in the clinical HLA laboratory are: HLA typing, HLA antibody screening/identification and crossmatching. When applied appropriately at the varying stages of transplant assessment their results may ascribe different risk states. While on the waitlist, the main risk question is how (immunologically) difficult will it be for a recipient to find a suitably (HLA) matched donor. This requires an understanding of the number and specificity of HLA antibodies in potential recipients compared to the HLA antigen frequencies in the larger potential donor population: HLA antibody screening and population level donor HLA typing is utilized, and if high risk (low donor access) is identified, increased donor priority may be given in allocation, or pre-emptive strategies to reduce or avoid antibodies can be employed [7–12]. Conversely, at the time of a potential transplant the critical issue is now whether a recipient has HLA antibodies directed specifically to the particular donor in question and all three platforms are now employed to estimate this risk of donor specific antibodies that can result in hyperacute, accelerated, acute and chronic rejection [13–15]. A high risk transplant can be avoided or immunosuppressive treatments can be augmented in an attempt to reduce this risk. Post-transplant, the development of memory alloimmunity or de novo HLA antibodies specific to the donor HLA typing indicate a higher risk of developing acute and chronic antibody mediated complications.

4. HLA typing

Traditional HLA typing for renal transplants centered on HLA-A, HLA-B and HLA-DR, partly due to methodological availability of reagents. Typing was performed by co-culturing recipient cells with known anti-HLA antibody sera combinations, and assigning type based on the pattern of cell death. This has since been superseded by the use of polymerase chain reaction (PCR) based technologies, predominantly reverse sequence specific oligonucleotide primer (R-SSO or sequence specific primer (SSP) based. Primers correlating with given HLA genotypes are used, so expansion of recipient DNA by PCR will only occur in the presence of a given type. Analysis of which primers lead to expansion allows identification of the HLA genotype. R-SSO and SSP technologies can provide a relatively rapid result within hours, and may be used to type an individual for all HLA proteins – A,B, Cw, DR, DRw, DQ, DP. Historically, the optimally matched kidney graft was considered to have 0/6 mismatches (defined by differences at 2 each of HLA-A, B, DR antigens), with the least well-matched having 6/6 mismatches. Long-term graft outcomes were reported by degree of mismatch, with a clear impact on longer-term survival [16–18]. All HLA proteins including HLA-Cw, HLA-DP and HLA-DQ are now recognized as antigenic targets with the potential for antibody formation and impact on subsequent graft survival [2,3,19–21]. Indeed, antibodies against HLA-DQ now form the majority of identified class II DSAs [22,23]. The potential number of mismatches is now much greater with up to two allele/antigen mismatches possible at each of the HLA-A*, B*, C* DRB1, DRB3/4/5* DQA1*, DQB1*, DPA1* DPB1* loci. These loci are now routinely used in allocation algorithms within the United States [24].

The transition from serological typing to molecular PCR-based typing allowed refinement and greater accuracy in HLA-typing. Serological methods rely on a whole-antigen–antibody reaction, and cannot easily discriminate between allelic variants which encode the same overall protein but may with potential for small but significant differences in immunogenicity. Conversely, specific molecular primers allow typing of allelic variants that may differ by as little as a single amino acid. For clarity, standardized HLA typing is utilized. An asterisk is used to

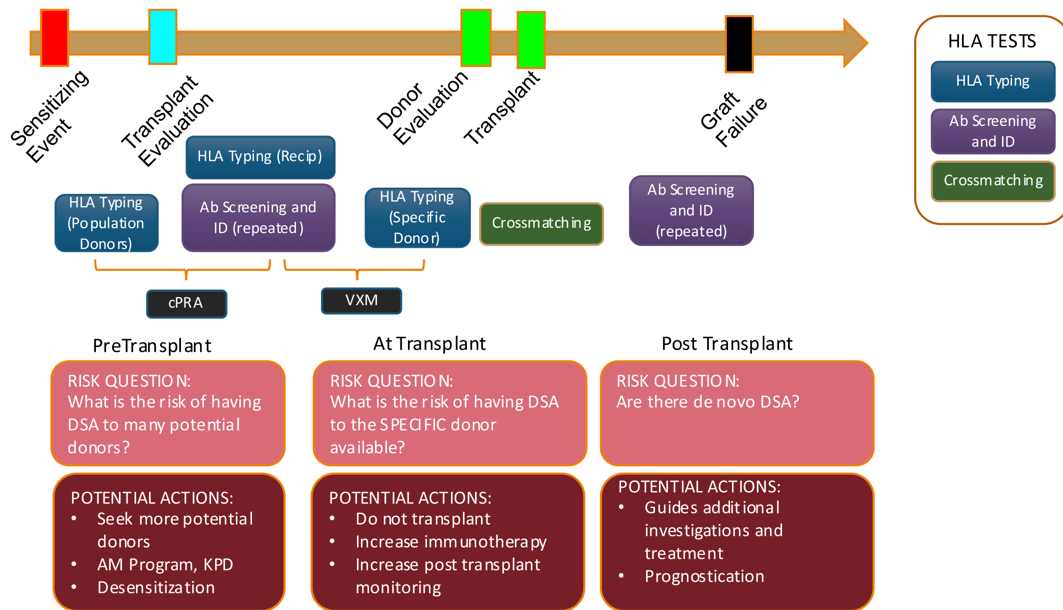

Fig. 1. HLA testing platforms and their application in transplant risk assessment. Three HLA testing platforms are predominantly used in transplant risk assessment. However, depending on the peri-transplant time point they may be applied in different combinations to assess risk. Each time period uses histocompatibility testing to assess specific and different types of risk. The potential actions that may result from a high risk state are correspondingly different also.

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