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# HLA Matching for Kidney Transplantation

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## INTRODUCTION

Histocompatibility testing is an essential component of a successful kidney transplant program for two fundamental reasons. First, human leukocyte antigens (HLA) play a central role in the cellular and humoral immune responses that determine the outcome of a transplant. Second, the extensive polymorphism of HLA poses a major barrier to successful transplantation. The role of HLA matching in renal transplantation is evolving as advances in immunology increase our understanding of the structure and function of HLA and as improvements in technology have enhanced our ability to distinguish HLA antigens and the antibodies reactive to them. Transplant success rates have increased markedly because of the development of better immunosuppression treatments for controlling the immune responses that lead to transplant failure. We now know that the benefit of HLA matching varies depending on donor and recipient risk factors. There are definite differences in the distribution of HLA alleles among various ethnic populations; therefore, allocation schemes weighted heavily for HLA compatibility will favor distribution to Caucasian recipients because the majority of deceased organ donors are Caucasian. Many argue that current immunosuppression regimens obviate the benefits of HLA matching altogether, raising the question of whether HLA matching should be used in allocation. In this article, we review potential effects of HLA on transplant immunity (summarized in Table 1), HLA matching protocols for kidney transplantation (Table 2), confounding factors for HLA matching (Table 3), and allocation issues (Table 4). Recommendations for HLA matching are provided after the conclusion.

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## HLA AND TRANSPLANT IMMUNITY

HLA compatibility affects transplant immunity in several ways (Table 1). First, HLA antigens can stimulate B cells to produce alloantibodies, which are involved with humoral mechanisms of transplant rejection. Recent studies have established histopathologic evidence of humoral rejection with immunostains specific for complement components (especially C4d) and immunoglobulins [1–3]. Although class I antigens controlled by the HLA-A, -B and -C loci are the primary targets of alloantibodies, emerging evidence indicates that antibody reactivity to class II antigens encoded by HLA-DR and HLA-DQ antigens may also result in graft loss [4–7]. In recent years, humoral immunity against HLA has been recognized as a major risk factor for chronic rejection and transplant failure [8, 9].

There are two general mechanisms for development of cellular immunity to HLA antigens [10–12]. Direct recognition is provoked by the interaction of recipient T cells with incompatible HLA antigens on the surface of so-called professional antigen-presenting cells (APC), primarily dendritic cells from the donor. The general result is a vigorous T-cell response with specificity for donor HLA antigens. Graft damage is mediated by allospecific effector T cells. These T cells infiltrate the graft and initiate transplant rejection [13–18]. It is thought that class I antigens mainly activate cytotoxic T cells, whereas class II antigens activate the helper and effector T cells that secrete inflammatory cytokines. On the other hand, an APC subset of dendritic cells can stimulate regulatory T cells, which promote transplant tolerance [19, 20]. Although most professional donor APC will disappear soon after transplantation, a small proportion may persist in the recipient. In some studies, microchimerism seems to correlate with the long-term success of a transplant [21, 22]. Recent research suggests that the recognition of donor HLA by alloreactive T cells in the epithelium and the vascular endothelium is an important step in the allograft response [23–25].

Indirect allorecognition is a mechanism of T-cell ac-

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**TABLE 1** Potential effects of human leukocyte antigen (HLA) on transplant immunity

- Humoral immunity
  - Against Class I HLA antigens
    - Complement-dependent antibodies
    - Complement-independent antibodies
  - Against Class II HLA antigens
- Cellular immunity
  - Direct allorecognition
    - Cytotoxic CD8 T-cells
    - Effector CD4 T-cells
    - Regulatory T-cells
  - Indirect allorecognition
    - Effector CD4 T-cells
- HLA-restricted immune responses
  - Antiviral immunity
    - Cytotoxic CD8 T-cells
  - Recurrent autoimmune disease
    - Effector CD4 T-cells

tivation, induced by recipient APC that present donor HLA antigens derived from the transplanted organ [26]. The uptake and processing of such antigens occurs through the exogenous pathway of antigen processing, whereby class II HLA molecules on recipient APC present donor-derived peptides to recipient CD4 T cells. Indirect T-cell alloreactivity can be long lasting because an *in situ* transplant is a continuous source of donor alloantigens. This mechanism may contribute to the development of chronic rejection [26–28].

HLA matching may have a dualistic effect on transplant outcome. On the one hand, it reduces alloreactivity and graft rejection; on the other hand, it may promote HLA-restricted immune mechanisms of graft injury secondary to infection [29, 30]. T cells reactive to microbial peptides presented by APC develop as individuals develop immunity to a viral infection. HLA matching may allow virus that has adapted to host HLA antigens to cause inflammatory damage to the transplant if infected transplanted tissue expresses the same HLA antigens as the recipient. In this scenario, HLA mismatches may promote detection of viral infection through presentation of nonadapted peptide-MHC complexes. There is ample evidence that HLA matching may increase the incidence of virus-induced injury in liver transplants [31–33] and some evidence in renal transplants [34–36]. HLA matching may also increase the risk of recurrent autoimmune disease. An example is the increased incidence of recurrent glomerulonephritis in kidneys transplanted from HLA-matched living related donors [37]. This increased risk might be attributable to familiar associations, but prompts the question of whether we should always strive for better matches.

Viral infection may also increase the importance of HLA matching. T cells reactive to viral peptides sometimes cross-react with HLA antigens, which could result in a heightened response to certain mismatches [38]. HLA matching may be of particular importance for seronegative recipients receiving organs from seropositive donors. Recent evidence suggests patients given a cytomegalovirus-positive graft who previously did not have exposure to the cytomegalovirus virus have poor outcome unless matched with donor DR antigens [39].

## THE CLINICAL REALITY OF HLA MATCHING

The utility of HLA matching is apparent from worldwide allocation policies for deceased donor kidney transplantation, which promote transplantation of zero-HLA-A, -B, and -DR mismatched candidates from national waiting lists. Such transplants have clearly superior outcome compared with outcomes for grafts with one or more HLA mismatches. Nevertheless, a significant proportion of these transplants fail—some because of nonimmunologic causes having to do with the quality of the kidney or recurrence of disease, others because of rejection resulting from allorecognition of donor incompatibilities. Potential incompatibilities may be due to different alleles of HLA-A, -B, and -DR loci, as discussed in the following section; differences in antigens at other HLA loci, such as HLA-C, -DQ and -DP; or other molecules not traditionally matched such as HLA class I heavy-chain molecules encoded by MICA [4, 40, 41].

Conversely, many mismatched transplants have long-term function with no evidence of rejection. Certain vascularized grafts can withstand antibody-mediated injury [42], with possible mechanisms including antigenic modulation [43], graft accommodation [44–46], and protection by anti-idiotypic antibodies [47–49]. Not every HLA mismatch induces antibody or effector T cells. Many reports describe different cellular mechanisms of long-term graft survival (even without immu-

**TABLE 2** HLA matching protocols for kidney transplantation

- Matching for HLA-A, -B, and -DR antigens
- Mismatching for HLA-A, -B, and -DR antigens
  - Broad vs split antigens
  - Acceptable and unacceptable mismatches for highly sensitized candidates
  - Permissible mismatches with graft outcome similar to nonmismatched transplants
- DR matching
- CREG matching
  - Public and private class I epitopes
- Structurally based matching
  - Amino acid residue mismatching
  - HLAMatchmaker

Abbreviations: HLA = human leukocyte antigen; CREG = cross-reacting groups of antigens.

**TABLE 3** Confounding factors

- Quality of donor kidney
  - Donor age: expanded criteria donors
  - Extended ischemia time
  - Living donors
- Recipient risk factors
  - Pediatric recipients
  - Ethnicity
  - Sensitization
  - Immunosuppression

nosuppressive drugs), including hematolymphoid microchimerism [21, 22], T-cell hyporesponsiveness [50], apoptosis [51], regulatory cells [52], and immunologic tolerance [22]. It also has been suggested that HLA-G, a minimally polymorphic HLA class I molecule, might protect transplants from rejection [53]. Thus, under specific but as yet undefined clinical conditions, certain HLA mismatches are permissible. It would be interesting to identify those HLA mismatches that elicit immune effector responses, which lead to rejection-related transplant failures.

Several investigators have attempted to determine mismatch permissibility—mismatches that do not elicit an immune response and so should not have an impact on transplant outcome [54–60]. One study considered that all recipient antigens may be important and defined immunogenic and permissible mismatches in the context the entire recipient A, B, and DR phenotype [61]. These results were confirmed in another registry analyses [62], and allocation to avoid these mismatches was suggested [63]. Subsequent studies with deceased donor transplant databases found superior graft survival for the permissible mismatch combinations [64, 65], but conflicting results were noted in another registry analysis [66]. Another approach suggested that noninherited maternal HLA antigens may result in mismatch permissibility through the development of prenatal tolerance [67, 68]. Registry analysis indicated one-haplotype mismatched related transplants that were mismatched for noninherited maternal HLA antigens had superior survival rates compared with those mismatched for noninherited paternal antigens [68–70]. But, again, these results were not validated in subsequent registry analyses [71–73]. Validation of mismatch permissibility models remains elusive.

HLA compatibility can also be defined in terms of mismatch acceptability—mismatches in allosensitized transplant candidates that result in a negative crossmatch [74]. In this context, unacceptable mismatches are antigens reacting with antibody detectable in the patient sera, whereas acceptable mismatches are those with no detectable antibody. Transplant centers have the option of maintaining a list of unacceptable mismatches for transplant candidates. This practice streamlines organ allocation by eliminating the need to crossmatch for donors with these antigens. The potential use of acceptable antigens to widen the search for suitable donors for broadly sensitized candidates is expanded further in the discussion on allosensitization.

## WHAT IS MEANT BY HLA MATCH?

For many years, the practice of HLA matching was based on counting the number of mismatched HLA-A, -B, -DR antigens of the donor (Table 2). Increasing numbers of mismatches resulted in progressively lower survival rates [75–78]. Although HLA antigens were initially determined by serologic typing methods using alloantibody, several laboratories now use more precise DNA-based typing technologies. Most HLA antigens have additional polymorphism in their DNA and corresponding amino acid sequences that cannot be distinguished with alloantibody. High-resolution DNA typing is used to distinguish allelic differences. More than 800 HLA-A and -B alleles and more than 400 HLA-DR alleles have been defined [79]. HLA matching at the allelic level is done for bone marrow transplantation because mismatched alleles appear to contribute to rejection or graft versus host disease [80]. Although many solid organ transplant programs use DNA typing for defining HLA antigens, alleles are not generally resolved, but rather low-resolution or generic typing is performed to determine HLA antigens at the level resolvable by alloantibody.

HLA antigens can be combined based on the historic process of naming antigens [81]. The terms *broad* and *split* antigens can be traced to the HLA naming system developed by the World Health Organization. In 1964, researchers gathered at the National Academy of Sciences in Washington, DC, to compare techniques used to identify allogeneic differences among humans and to share alloantibody to compare techniques. During the Second Histocompatibility Workshop convened in Leiden in 1965, 10 sets of alloantibody reactivity defining initial HLA antigens roughly were recognized. These antigens roughly correspond to crossreacting groups of antigens (CREGs) discussed in the following section.

**TABLE 4** Allocation issues

- Wait list size
  - Potential to match
  - Maintaining large waiting lists
- Change in human leukocyte antigen points for local allocation
- Highly sensitized patients
- Number of human leukocyte antigen antigens used to match
- Priority for uncommon phenotypes

When the first World Health Organization nomenclature meeting was held in Los Angeles in 1970, 27 antigens were defined. The process of defining new antigens involved extensive screening of sera to find alloantibody reactive to subsets of individuals having known antigens. These alloantibodies split previously known broad antigens into two or more antigens. For instance, when a serum was identified that reacted only with a subset of cells known to have A9, A9 was split to A23 and A24 [82]. Similarly, DR2 was split to DR15 and DR16. HLA matching criteria can vary depending on consideration of broad or split antigens. For instance, with broad DR matching, a donor with DR15 would be considered equivalent for a recipient with DR16 because both antigens are splits of the broad antigen DR2.

The United States and Europe differ slightly in approach when considering broad and split antigens for kidney allocation. The United States uses 94 antigens, (25 HLA-A, 51 HLA-B, and 18 HLA-DR) [83], while Eurotransplant (Germany, The Netherlands, Belgium, Luxembourg, Slovenia, and Austria) considers 51 antigens (10 HLA-A, 25 HLA-B, and 16 HLA-DR) [84] and the United Kingdom uses 49 antigens (11 HLA-A, 26 HLA-B, and 12 HLA-DR) [85]. Furthermore, candidates with one A- or B- locus mismatch (but zero DR mismatches) are considered HLA matched in the United Kingdom. Increased utilization of broad antigens increases the probability of identifying an HLA matched [86–88] recipient for a donor. This strategy has the potential for increasing the percentage of transplants allocated to HLA matched recipients in the United States.

Split antigen matching may be more important for HLA-A and -B antigens than it is for DR antigens. Zero HLA-A-B-DR mismatched recipients with split HLA-DR mismatches had survival similar to those with no split DR mismatches; but those with split HLA-A or -B antigen mismatches had poorer survival [89]. Similar results were noted for first transplants in Europe [75], although recipients with a previously failed transplant had poorer outcome with split DR mismatches.

In the early and mid-1990's there was concern regarding the quality of HLA typing. An analysis of donor antigens in zero mismatched transplants revealed a 30% discrepancy rate in retyped antigens [90], mostly due to differences in reporting broad and split antigens. Studies from Europe indicated a 25% discrepancy rate between HLA types defined by serology and retyped using DNA methods [91–93]. By 1998, discrepancy rates for DR antigens were less than 10% [94].

The importance of HLA-DR matching in renal transplant outcome was apparent even in early examinations [95]. Recipients matched for DR split specificities had a lower incidence of delayed graft function when there is extended ischemia [96], so some centers allocate kidneys based on genomic DR compatibility [97]. Repeat donor HLA-DR mismatches have led to lower graft survival rates in patients who are retransplanted [98, 99]. The influence of HLA-DQ matching is less clear. Some studies found a beneficial effect [100–102], but others did not [103–105]. A similar controversy exists concerning the effect of HLA-DP matching [106–108].

Another level of matching considers cross-reacting groups (CREGs) of HLA-A and -B antigens. Immunization against an HLA antigen often results in antibodies that bind not only the immunizing antigens, but also with sets of structurally similar antigens [109–111]. The portion of an HLA antigen that is recognized by antibody is referred to as the antibody epitope. CREGs share one or more antibody epitopes. There are considerable differences in the HLA antigen frequencies between African-Americans and Caucasians [112], but CREGs are more evenly distributed [113, 114]. An allocation variance based on CREGs was adopted by the United Network for Organ Sharing (UNOS) in 1999 [81]. The rationale for adopting the CREG model was the increased probability for identifying more compatible kidneys for ethnic minorities [115].

Whether CREG matching improves graft outcome is controversial. Several studies found CREG matching resulted in graft survival rates comparable to survival for those allocated with zero HLA-B and -DR mismatches [87, 88, 116–118]. However, other studies found a benefit only for transplants with one HLA-A or -B mismatch [119–121]. Results from prospective CREG matching trials are inconclusive [122]. The number of patients receiving zero CREG-mismatched grafts was less than anticipated, probably because of the limited number of waiting recipients in most of the participating allocation areas. The controversy regarding CREG matching stems, in part, from the difficulty of defining the exact spectrum of CREGs. The UNOS CREG-matching algorithm does not consider many CREGs, which may have an impact on graft outcome [88, 123]. Furthermore, several studies suggest certain CREGs may be more immunogenic than others, in that they are more likely to elicit an immune response [124, 125].

More complex models could include more CREGs, define CREGs based on antibody epitopes, match for DNA-defined alleles, or include antigens encoded by other loci such as HLA-C, -DQ, and -DP. These methods could increase the degree of compatibility or stringency of HLA match and perhaps result in graft survival comparable to that observed with HLA-identical sibling transplants [78]. However, fewer recipients would be HLA matched.

### HLA Matching and Transplant Outcome

Historically, registry analyses have demonstrated a benefit of HLA matching for renal transplantation. Before 1985, the 1-year loss rate for HLA-matched grafts in the United States was 17% compared with 42% for those with six A, B, and DR mismatched antigens (a 25% difference) [77]. In 1990, this difference decreased to 17% [126]. In 1995, the loss rate was 10% for HLA-matched and 18% for HLA-mismatched transplants [126]. In 2001, only 7% of HLA-matched and 12% of HLA-mismatched transplants were lost—a fourfold decrease from 1985 [127]. Although the loss rate declined markedly in the epochs since 1985, the relative rate of loss remains approximately twice as high for mismatched transplants.

There are those who question whether a 5% difference in loss rate after 1 year is clinically significant. However, this difference increases with time after transplantation and becomes more striking when assessing long-term outcome. Half-life estimates [76], based on the rate of graft loss after the first year, indicate that HLA-matched grafts function 50% longer than those with mismatches [128]. Ten-year survival for zero mismatched transplants performed between 1979 and 1984 was 41% compared with 25% for those with five to six HLA mismatches [129]. Interestingly, an identical 16% difference in the estimated 10-year survival for zero and five to six mismatched transplants was projected for transplants performed between 1995 and 2000 (63% versus 47%, respectively).

Factors including ethnicity, age, diabetes, sensitization, previous transplant of the recipient, donor age, cause of death and ischemia time, transplant center, and year all influence graft outcome [128]. After adjusting for these confounding factors, the hazard ratio of graft loss for HLA-mismatched kidneys compared with those with zero A, B, and DR mismatches was 1.38 (95% confidence interval 1.31–1.46, $p < 0.001$). After censoring death with function, the hazard ratio for HLA-mismatched transplants was 1.55 (1.45–1.65, $p < 0.001$) [128]. Rejection is another measure of outcome used to assess the efficacy of HLA matching.

A comparison of paired kidneys, in which one kidney was transplanted in an HLA-matched recipient and the other in a mismatched recipient, found that those receiving an HLA-matched transplant had a 6% lower incidence of rejection (13% versus 19%) [128]. Rejection episodes during initial hospitalization can delay discharge and increase costs [130]. Rejections are associated with lower survival and increased amounts of immunosuppression, which may increase the risk of infection or malignancy. Acute rejection is associated with increased risk of chronic rejection [131–133], which is one of the leading causes of late graft loss. DR mismatches are associated with a increased risk of acute rejection and early graft loss [130, 134–136]. There is some evidence that HLA-A and HLA-B antigen mismatches are associated with late graft loss [137–139]. Costs related to transplantation have been estimated in recipients with primary Medicare insurance coverage [140]. Such assessment of economic outcome captures the effect of adverse events that lead to hospitalization, dialysis, or immunosuppression. A recent study estimated 3-year costs for HLA-matched transplants at $60,436 compared with $80,807 for mismatched transplants.

## KIDNEY ALLOCATION FROM DECEASED DONORS

In the United States, the HLA antigens for each of the 55,000 waiting candidates are compared with donor antigens; any candidate with zero HLA-A, -B, or -DR antigen mismatches is given priority for a kidney [83]. When rules for allocation were first formulated in 1987, all six donor and recipient A, B, and DR antigens were considered for a match and only 2% of kidneys were matched. In 1990, the criteria for HLA matching changed to allow matching of homozygous donors and recipients. This change increased the percentage of HLA-matched kidneys to 7%. In 1995, criteria changed to consider HLA mismatches rather than matches. Donors with one antigen at a locus could be matched to recipients with two antigens at that locus. With mismatching, the proportion of HLA-matched transplants increased to 15% [89]. The change to a mismatch policy nearly doubled the percentage of shared organs allocated to African-Americans from 5.5% to 10.5% [141].

The probability of transplanting an HLA-matched kidney is proportional to the number of candidates considered. For example, if allocation were restricted to a local allocation area, one with 2,000 candidates awaiting transplantation, only about 2% of transplants would be HLA matched [142]. One of the most important advances facilitating HLA matching was the development of cold storage methods that allow shipment of donor kidneys over long distances. This advance enabled the development of national waiting lists in which candidates on one side of the country could receive zero-mismatched kidneys procured from the other side of the country (Table 4). However, national data indicated an inverse correlation between renal transplant survival and cold ischemia time at all levels [143], and ischemia time longer than 24 hours is associated with lower graft survival [144].

When there are no candidates for a zero-mismatch kidney, patients in the local allocation area are ranked by a point system that assigns priority based on the degree

of HLA antigen match, time waiting, allosensitization, and, for pediatric candidates, age [83]. Until 2003, HLA match points were assigned to candidates based on the number of B and DR antigen mismatches, but this policy recently changed. Candidates with 0 and 1 DR mismatch receive 2 and 1 points, respectively, because recent data suggest very little benefit from HLA-B antigen matching, which reduces access to transplantation for ethnic minority groups [145]. As noted in previous allocation simulations [86–88] and in the prospective CREG allocation variance [122], the percentage of HLA-matched transplants increases with the size of the sharing area. Therefore, it may be possible to increase the percentage of 0 DR-mismatched transplants by increasing sharing from local areas to wider regions.

The number of patients awaiting kidney transplantation has increased dramatically during the past decade. Between 1992 and 2001, the number of patients awaiting transplantation more than doubled in the United States from 22,000 to 51,000 [127, 146]. In contrast, the number of deceased donor kidney transplants increased by only 1000 (from 7200 to 8200). This imbalance between the number of candidates and transplant volume has increased the waiting time for a transplant. The proportion of patients waiting longer than 2 years increased from 26% to 40% during this period.

Maintaining patients awaiting transplantation is resource intensive. For example, a yearly cardiac stress test is recommended for older candidates to assure that they remain medically suitable for transplantation. At many large transplant centers, only 10–20% of candidates receive a transplant per year. Considerable cost savings could be achieved if resources are focused on those most likely to receive a transplant [147]. Certain individuals have a high probability of receiving an HLA-matched graft because they have HLA antigens that are common in the population [148, 149]. By assessing this probability, it is possible to focus resources on candidates likely to receive an HLA-matched graft.

The probability of finding a donor can also be used to increase access for individuals with uncommon or disadvantaged phenotypes. Homozygous individuals with only one antigen at the A, B, or DR loci illustrate the point that certain HLA phenotypes result in a similar disadvantage as that associated with the O blood group when considering access for blood transfusions. Just as A, B, and AB blood group individuals are compatible with O donors, individuals with two antigens at the locus are considered compatible if they share an antigen and therefore are not mismatched with a donor. This situation may lead to an accumulation of homozygous individuals waiting for a transplant because their matched donors are considered compatible with individuals with different phenotypes. In 1998, the United Kingdom incorporated a probability for finding a match into their allocation algorithm [149].

## LIVING DONOR RENAL TRANSPLANTS

HLA matching was thought to be very important for living donors, given that two-haplotype–matched sibling donors have the best outcome (Table 3). However, in the mid-1990s, results from a large registry analysis found that transplants from two-haplotype–mismatched siblings or spouses had outcomes similar to one-haplotype–mismatched sibling or parental donor transplants. Furthermore, HLA-mismatched living donor kidneys had superior outcome compared with HLA-matched deceased donor transplants [150, 151]. A fit-and-match hypothesis was proposed to explain the discrepancy that one- and two-haplotype mismatched kidneys from living donors had similar survival to zero-mismatched cadaveric kidneys [152]. Damage resulting from increased cold ischemia or donor age decreases the number of functioning nephrons. The fit-and-match hypothesis suggests that the impact of HLA matching on graft outcome is dependent on the "fitness" of the kidney, which is reflected by the number of functioning nephrons. Kidneys with only a small fraction of functioning nephrons are less tolerant of the further loss of nephrons that result from acute or chronic rejection. Because HLA matching decreases the probability of rejection, it was thought that HLA matching would be much more important for these kidneys. This hypothesis could explain the difference in HLA matching effect for living and deceased donors. Only healthy individuals are allowed to be living donors; the process of death releases cytokines that damage kidneys from deceased donors [153].

The use of living donors for renal transplantation has grown steadily during recent years. In 1992, about one-third of renal transplants were from living donors, whereas, in 2001, the number of living donors was actually greater than the number of deceased donors [127]. Eighty percent of the increase was due to increased usage of two-haplotype–mismatched kidneys from sibling, spouse, and unrelated donors [150]. Living donors are often considered a first option for renal transplant candidates in the United States.

### Expanded Criteria Donors

The fit-and-match hypothesis suggests the importance of HLA matching should be greater for kidneys from older donors. However, this is not the case. The benefit of HLA matching is much smaller with kidneys from older donors [154]. In fact, mismatched kidneys from younger donors actually had superior outcome when compared with HLA-matched kidneys from older donors. Adjusted 5-year survival was 51% for HLA-matched recipients

when the donor was older than 60 years compared with 64% for mismatched donors younger than age 40 [155]. It has been suggested that kidneys from older donors have increased risk of nonimmunogenic graft loss and should be allocated to older recipients [156]. Recent data from Europe suggest that age matching for older donors and recipients results in outcomes comparable to HLA matching [157]. Avoiding extended ischemia time had a greater impact on outcome than avoiding DR mismatches [158].

Early in 2003, UNOS adopted a policy to exclude expanded criteria donors from the national HLA matching policy and instead allocates these kidneys to candidates who consent to receive such organs. Criteria for expanded donors were established using factors that resulted in a 70% increased risk in graft loss [144, 159] and included donors older than age 60 and those ages 50–59 with at least two of the following characteristics: hypertension, serum creatinine greater than 1.5 dL/mL, and cerebrovascular cause of death. Approximately 15% of donor kidneys fit these criteria [160]. A recent conference examining optimal use of these kidneys recommended that candidates older than age 60, diabetic candidates older than age 40, and those fairing poorly on dialysis would most likely receive benefit from expanded donor kidneys [144, 160]. A recent study reevaluated whether recipients of expanded criteria donor kidneys had a survival benefit compared with similar patients on the waiting list. It confirmed a clear and large benefit from expanded criteria donor transplants compared with no transplant, although it took somewhat longer (14 months) posttransplant to reach the point after which cumulative patient survival was superior [161].

### Pediatric Recipients

Under the current US allocation algorithm, pediatric candidates younger than age 11 years receive four extra points and those ages 11–18 years receive three extra points [83]. The median waiting time for pediatric candidates is approximately 1 year compared with 3 years for candidates 35–49 years of age [162]. This decreased wait also decreases the opportunity for pediatric candidates to receive an HLA-matched kidney. Less than 3% of pediatric recipients receive a zero-A, -B, or -DR–mismatched transplant [163] compared with 15% for adult recipients [128]. Organs from living donors, particularly parents, are more commonly used for pediatric candidates. A report from the North American Pediatric Renal Transplant Cooperative Study found 43% of donors for pediatric recipients were living donors. Interestingly, however, deceased donor grafts with zero HLA mismatches had similar outcome compared with those from living donors [163].

## HLA MATCHING FOR ETHNIC MINORITIES

HLA matching is often cited as a primary reason for inequitable access to kidney transplants in ethnic minorities [164, 165]. This inequity is disproportionately borne by African-Americans and other patients with uncommon HLA types. African-Americans have longer waiting times [164, 165] and rarely receive HLA-matched kidneys [165, 166]. Between 1987 and 2000, African-Americans received only 8% of the HLA-matched kidneys and 25% of the kidneys with HLA mismatches [128]. This difference is due partly to the majority of deceased kidney donors (85%) being Caucasian [127] and the distribution of HLA antigens differs among different ancestry [112, 114, 167]. Furthermore, there is greater diversity of HLA antigens among African-Americans when compared with Caucasians. An examination of individuals waiting for a transplant revealed 98% of the African-Americans waiting for a transplant in 1991 had unique HLA phenotypes compared with 85% of Caucasians [168]. Only 5 of the 79 HLA-A and -B locus antigens are shared in both 5% or more of African-American candidates and Caucasian donors [114, 169]. Estimates from the National Marrow Donor Program indicate the probability of finding a match among half a million individuals was 16% lower for African-Americans compared with Caucasians (61 with 77%) [170], and the probability of a match between Caucasian donors and African-American recipients was only 18%.

A recent report indicated that African-Americans on renal dialysis were 41% less likely than Caucasians to be placed on the waiting list, and those on the waiting list were 45% less likely to be transplanted [171]. The proportion of ethnic minorities waiting for a transplant in the United States has grown steadily, from 35% in 1992 to 45% in 2001 [127, 146]. The higher incidence of sensitization before transplantation in African-American patients presents another obstacle for transplantation [172]. Inequitable access to the waiting list also was noted for other groups, including non-Caucasian ethnicities, women, diabetics, and candidates older than age 40. Decreased access for these disadvantaged groups was attributed to ABO blood group differences, uncommon HLA phenotypes, and allosensitization.

The benefit of HLA matching was somewhat smaller for African-American recipients than for Caucasians. The half-life for HLA-matched African-American recipients was 7.7 years compared with 5.7 years for those with mismatches or 35% longer for matched transplants [128]. In comparison, Caucasian recipients had 43% a longer half-life (12.9 versus 9.0 years for HLA-matched transplants). The lower half-lives in African-Americans may be due to an increased risk of nonimmune graft loss. The half-life for hypertensive African-Americans receiving HLA-matched kidneys was 5.2 years compared with

10.8 years for African-Americans with other causes of end-stage renal disease.

### The Highly Sensitized Patient: Match or Treat?

Humoral sensitization, the development of antibody reactive to HLA antigens, often occurs after pregnancy, transfusion, or a lost transplant. PRA (panel-reactive antibody), the percentage of an HLA-typed panel reactive to a patient's serum has historically been used to describe the degree of sensitization. A recent review article describes various methods for assessing sensitization in patients being evaluated for a transplant [173]. A crossmatch test is performed before transplant to ensure that the patient does not have antibody reactive to donor antigens. It is difficult to find crossmatch-negative, HLA-compatible donors for highly sensitized patients with >85% PRA. The accumulation of highly sensitized patients on kidney transplant waiting lists represents a growing problem for many transplant programs.

Several strategies have been used to enhance transplantation of highly sensitized patients. One is to maintain screening trays that include the sera of all sensitized recipients in an allocation area [174–177]. Another approach uses extensive serum screening to identify acceptable mismatches (*i.e.,* antigens not reactive to patient sera [178]). The Acceptable Mismatch program, implemented by Eurotransplant more than 10 years ago, shortened the waiting time and increased the transplantation rate for highly sensitized patients [74]. Outcome in sensitized patients receiving an HLA-matched kidney was significantly better than for those receiving mismatched grafts [85, 128, 179]. Moreover, transplanted patients did not require more immunosuppression [180].

Another approach for transplanting highly sensitized patients is to remove or reduce the titer of donor-specific antibodies before transplantation using exchange plasmapheresis [181–183], intravenous immunoglobulin [184, 185], or a combination of these procedures [186]. The goal of these techniques is to convert the crossmatch of an HLA-mismatched donor from positive to negative so a transplant can be performed. Although these protocols have significant success rates, there are a number of drawbacks. Intravenous immunoglobulin sometimes fails to sufficiently reduce the level of high-titered antibody [187]. And because antibody typically rebounds after pheresis, this procedure is appropriate only when a living donor is available [188]. Furthermore, these procedures are expensive and resource intensive. Although antibody removal allows transplantation of sensitized recipients, an HLA-matching scheme that optimizes identification of crossmatch negative donors may be a more effective strategy.

## ORGAN ALLOCATION FOR HIGHLY SENSITIZED TRANSPLANT CANDIDATES

Highly sensitized transplant candidates have the longest waiting time for transplantation. Candidates registered for a renal transplant in 1997 with peak PRA between 20% and 80% had a median waiting time of 1632 days compared with 689 days for those with PRA <20% [127]. The median time could not be calculated for candidates with PRA >80% because fewer than 50% were transplanted. In the United States, broadly sensitized candidates receive four extra points to improve their ranking on the waiting list, but this strategy does not have much impact on transplant rates because of the extremely small probability of finding a suitable donor in a local allocation area. A recent study found that half of highly sensitized patients had a less than 1 in 10,000 chance of receiving a transplant [189]. Listing acceptable antigens would greatly increase the probability of finding a donor if these antigens were considered HLA matched [74, 180]. National sharing based on acceptable antigens seems reasonable, assuming the assessment of acceptable antigens is rigorous enough to assure a negative final crossmatch [189]. Such a program has been adopted by Eurotransplant [180]. The determination of acceptable HLA antigens requires intensive serum analysis efforts with well-defined HLA-typed panels.

## STRUCTURALLY BASED HLA MATCHING

Structural epitopes may better assess compatibility between donors and recipients than the conventional method of counting the number of HLA-A, -B, or -DR mismatches. As previously discussed, CREG matching offers an alternative strategy for organ allocation that permits greater access to better-matched organs, especially for minorities [190]. One difficulty that remains is lack of a precise definition of public epitopes. In prior analyses of epitope matching, the amino acid sequences of donor and recipient alleles were inputed and the most common allele was used for antigens reported in the UNOS or Eurotransplant registries [114, 189, 191–198]. More precise estimates would be possible if HLA alleles were determined for recipients and donors using DNA typing. Studies using HLA-specific monoclonal antibodies indicate that epitopes correspond to distinct amino acid residues or short sequences in HLA molecules [199–207]. These epitopes have been used as the basis for defining acceptable mismatches [199, 208–211]. Retrospective registry analysis indicates that epitope matching could be used to provide compatible kidneys for highly sensitized patients [211]. Other structurally defined parameters, such as peptide motif matching, may also influence renal graft outcome [88, 191, 212, 213].

A publicly available computer algorithm, HLA-

Matchmaker, can further augment the number of acceptable antigens for highly sensitized patients [123]. This algorithm considers each HLA antigen as a string of polymorphic amino acid triplets in antibody-accessible positions in the molecular structure. Through intralocus and interlocus comparisons, HLAMatchmaker assesses histocompatibility by determining which triplets on mismatched HLA molecules are different or shared between donor and patient. Antigens with no or few triplet mismatches are structurally similar to recipient antigens. Registry analyses indicate that transplants with no or few triplets mismatched have survival rates similar to zero HLA-A, -B, -DR mismatched transplants [196]. Analysis of recipients who experienced graft rejection suggest those with few triplet mismatches were less likely to become highly sensitized [197]. The beneficial effect of triplet matching applies to both nonsensitized and sensitized patients and also to Caucasian and non-Caucasian patients. Furthermore, transplants with 10 or more triplet mismatches had poorer outcome compared with those with four HLA-A and -B locus mismatches, suggesting allocation based on triplet mismatches may better identify transplants with high immunologic risk [196]. Triplet matching is also useful in corneal transplantation [161] and platelet transfusions of highly sensitized thrombocytopenic patients [214]. HLAMatchmaker permits a more effective analysis of HLA antibody reactivity patterns [195, 215] and increases the efficiency of finding acceptable mismatches for highly sensitized patients [180, 189, 197].

## CONCLUSION

Despite significant improvement in renal transplant outcome over the past 30 years, HLA matching remains one of the most important modifiable factors for reducing the risk of renal allograft loss. HLA matching decreases the risk of graft lost by about 40%. This degree of benefit, however, is not expected for expanded criteria donors. Furthermore, individuals with uncommon HLA antigens are less likely to receive an HLA-matched graft. A system that calculates the likelihood of future HLA-matched deceased donor kidneys for HLA phenotype combinations would help to facilitate informed choices by physicians, especially in the case of expanded criteria kidneys or for pediatricians who because of the increased allocation points given to their patients, have more choice in acceptance of kidneys. Finally, HLA matching could be further improved by determining mismatch combinations likely to result in a cellular or antibody-mediated graft rejection.

## RECOMMENDATIONS

1. Zero HLA-A, -B, -DR mismatched transplants should be performed when possible, but not at the expense of extended ischemia for expanded criteria donors.
2. Future HLA-matching systems should consider similarities in HLA structure among antigens and attempt to improve access for patients with rare phenotypes and all ethnic backgrounds.
3. A national sharing agreement based on acceptable mismatches should be implemented to increase transplantation rates of highly sensitized patients.
4. DNA typing should be used to better assess donor and recipient HLA antigens.
5. A review of DR matching beyond local sharing areas should be considered.

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