INTRODUCTION — The evidence that antigens of the HLA system provide the major barrier to acceptance of renal transplants was first obtained with living-related donor transplants. Graft survival was superior in sibling pairs having both the same serologically defined HLA antigens and a nonreactive in vitro mixed lymphocyte proliferative response when compared to randomly matched cadaveric donors treated with the same immunosuppressive drugs, principally azathioprine and prednisone. (The mixed lymphocyte response [MLR] is an in vitro estimate of incompatibility in which the degree of proliferation of the recipient lymphocytes to donor lymphocytes is measured.) There was an intermediate level of graft survival in haploidentical parent to child or sibling to sibling transplants, in which one but not both of the haplotypes matched.

The most valuable data bases now in existence are those representing pooling of information from a large number of collaborating centers. Although such pooled data may suffer from variations in protocols and undocumented selection factors, the power of univariate analyses becomes compelling when thousands of patients are included. These large databases include the United Network for Organ Sharing (UNOS), the Collaborative Transplant Study (CTS), Scientific Registry of Transplant Recipients (SRTR), the American Southeast Organ Procurement Foundation (SEOPF), the United Kingdom Transplant Service, Eurotransplant, and others.

RELATIVE IMPORTANCE OF HLA-A, -B, AND -DR — The simple assumption that each mismatch for HLA antigens has equal weight has not been borne out. The initial CTS analysis showed that the major impact comes from the DR and B antigens, with little additional effect from the A antigens [1,2]. The UK Transplant data was somewhat similar, with DR matching having a much greater effect than that of B or A [3]. Another study found that HLA-DR mismatches (and the number of rejection episodes) correlated with poor long-term survival [4]. Each antigen also appears to exert its effect at different times post-transplant, with the maximal effect of DR and B mismatching occurring within the first 6 months and 2 years post-transplant, respectively [5].

A related issue is whether specific HLA mismatch combinations are associated with decreased renal allograft survival [6,7]. A retrospective study addressed this issue by examining 2877 unrelated renal transplants with one mismatch of either HLA-A, -B, or -DR [6]. Seven unique combinations ("taboo" mismatches) of recipient HLA antigen and donor HLA antigen were associated with significant decreases in graft survival when compared to survival among transplant groups with either no mismatch or one indifferent mismatch. At five years, graft survival among the groups without a mismatch, with one indifferent mismatch, or with one taboo mismatch was 72, 69, and 50 percent, respectively. The mechanism by which "taboo" HLA mismatches may result in diminished allograft survival is unknown.

When trying to match a donor to a recipient, avoidance of mismatches is used in preference to matching of HLA antigens. This approach maximizes the number of patients offered well-matched grafts because the same antigen may be present twice. As an example, HLA-A2 is a common antigen and homozygosity is frequent.
Such a patient can receive a graft with no mismatches; however, he or she cannot
be matched for six HLA antigens, since only five are present.

**IMPORTANCE OF EARLY REJECTION EPISODES** — Long-term graft survival may also
be related to the presence or absence of early rejection episodes. Some findings
suggest that early rejection increases the risk of future graft failure, which is less
likely to occur with reduction in the HLA barrier.

It is of interest that the degree of mismatching per se is not directly predictive of
early rejection episodes. This raises the issue of whether intrinsic responsiveness of
individual patients determines to a large extent the rejection episode rate; once
rejecting patients declare themselves, the HLA barrier then becomes an important
determinant of graft survival rates. Alternatively, the rejection tempo may be
intrinsically more powerful with a higher number of mismatched antigens.

Failure to have an early rejection episode, on the other hand, may be determined
both by individual susceptibility to immunosuppressive agents and by
immunogenetic factors that vary with different donor-recipient combinations. A
relatively common example of the latter is the patient doing well with a second
transplant after vigorous rejection of a first graft bearing different HLA antigens.

**LONG-TERM GRAFT SURVIVAL** — Most transplants that are lost to acute rejection do
so within the first year; later graft loss is primarily due to chronic rejection, a
disorder that is not very responsive to current immunosuppressive regimens. (See
“Chronic renal allograft nephropathy”).

Multiple analyses have demonstrated improved survival in well-matched cases
[8,9]. In the 2005 annual report of the Scientific Registry of Transplant Recipients,
the five-year deceased non-extended criteria donor allograft survival for zero
versus six HLA-mismatched cadaveric kidneys was 74 and 65 percent, respectively
[10].

Long-term survival is also best in HLA-identical, particularly living related, kidneys
and worst in randomly matched cadaver kidneys [8,9]. As an example, a report
from the same UNOS database evaluated more than 7600 HLA-matched (ie, no
mismatches) and 81,000 HLA-mismatched cadaveric renal transplants performed
between 1987 and 1999 in the United States [9]. HLA-matched transplants had
longer allograft half-lives (12.5 versus 8.6 years) and increased ten year survival
(52 versus 37 percent). Similar findings have been reported in subsequent years
[10].

The beneficial effect of HLA matching on long-term survival has come during the
cyclosporine and tacrolimus era, a period in which graft survivals and rejection rates
have continued to improve [11]. The benefits of HLA matching have also continued
with the introduction of mycophenolate mofetil and other agents [12].

The improved long-term survival observed in well-matched HLA grafts may be less
apparent in transplant recipients with a primary glomerular disease. In one report
of 60 patients in whom an HLA-identical living related donor transplant had been
performed, allograft survival was correlated with the original renal disorder [13].
Among the 33 patients with an underlying glomerulonephritis, the 5, 10, and 20
year graft survival was 88, 70, and 63 percent, respectively; by comparison, no
case of graft loss was observed among the remaining patients with nonglomerular
renal disease. Recurrent disease appeared to be the principal cause of graft loss.
Despite the importance of HLA-DR matching, some seemingly well-matched kidneys are still rejected. These findings in part reflect the incomplete accuracy of routinely used tissue typing methods.

A limitation of tissue typing is the difficulty in finding well-matched kidneys. The American UNOS program mandates that six-antigen matched grafts be given priority. Despite the large registered waiting list and relative ease of shipping kidneys around the country, only 13 percent of recipients of deceased donor kidneys are well-matched [9].

Priority shipping of organs is not limited to six antigen matched grafts as zero mismatching is also given priority. This occurred following two amendments to the original ruling by UNOS; the first to allow donors and recipients that were both homozgyous for one antigen to be considered phenotypically matched, and the second to allow for the shipment of zero mismatch kidneys. With zero mismatched kidneys, the donor does not express any antigen different from the recipient, although the recipient may have an antigen that is not expressed by the donor [9].

Most of the worldwide data on cadaveric transplantation has therefore been based upon random assignment of cases without regard to HLA incompatibility, and the importance of lesser degrees of matching has only been determined after transplantation. A strategy to increase the frequency of partially matched grafts and therefore of transplant survival is regional organ sharing, although the results are less dramatic compared to the six antigen matched cases. (See "Organ sharing in kidney transplantation").

Patients with greater than 36 hours of cold ischemia time may not benefit from HLA matching. In an analysis of the UNOS data base, recipients of zero HLA mismatched kidneys with less than 36 hours of cold ischemia time had superior five-year graft survival than recipients with one or more mismatches (75 and 67 percent, respectively, p<0.001) [14]. However, no survival advantage was observed if zero mismatched kidneys were exposed to more than 36 hours of cold ischemia time.

Thus, if there were no cold ischemia time effects, a strategy of national allocation and shipping of all kidneys (not just zero antigen mismatches) to minimize HLA mismatches would generate the largest graft survival improvement and cost savings [15]. However, there would be longer preservation times under a national allocation policy, and prolongation of cold ischemia time negatively affects outcome and costs.

Limited evidence suggests that the importance of HLA matching for allograft survival may have diminished over the last several years, with non-immunologic factors assuming more relative significance. One study, for example, evaluated the factors underlying allograft survival over the period 1994 to 1998 among over 30,000 transplant recipients of cadaveric kidneys [16]. With each successive year, ever increasing degrees of HLA mismatching was required to have a statistically significant adverse effect upon allograft failure. Thus, increased allograft failure was significantly associated with the following:

- Three to six antigen mismatches in 1995
- Four to six antigen mismatches in 1996
- Five and six antigen mismatches in 1997
- Six antigen mismatches in 1998

By comparison, peak panel reactive antibody, donor age, sex and cause of death, cold ischemia time, and donor and recipient body size, retained their relative
importance for allograft survival over this period. Although the reasons are unclear, the administration of increasingly better immunosuppressive regimens during this period may in part underlie these observations.

**HLA AND ORGAN ALLOCATION IN BLACKS** — In the United States, the distribution of HLA antigens and frequency of deceased donor donation differs among racial groups, thereby affecting organ allocation. Nationally, 17 percent of all non-extended criteria deceased donor kidneys are transplanted into fully matched recipients, of whom approximately 90 percent are white and only 9 percent black. Between 1987 and 1995, black patients received only 6 percent of fully matched kidneys despite constituting approximately one-third of the national waiting list. Conversely, 30 percent of partially or fully mismatched kidneys go to black recipients, approximating the frequency with which blacks appear on the waiting list.

To address this relative inequity, the national allocation policy of the United States was changed to no longer give priority points for fewer HLA-B mismatches. This was derived in part from findings of a study that addressed the effect of eliminating HLA-B matching. Based upon a Cox model analysis in which HLA-DR but not HLA-B matching was utilized, the number of transplants was calculated to decrease by 4.0 percent among whites but increase by 6.3 percent in nonwhites; this change was determined to result only in a 2.0 percent increase in graft loss. By comparison, removal of both HLA-B and HLA-DR would result in an 8.0 percent increase in graft loss. A study modeling the impact of this policy demonstrated that it would result in a detrimental effect on Caucasian survival and overall increased costs. (See "Organ sharing in kidney transplantation")

**LESS SPECIFIC HLA MATCHING** — As mentioned, because the distribution of HLAs differs across ethnic groups, African-American and other minority recipients receive a smaller percentage of organs than do their white counterparts. An alternative to allocation based upon HLA specificities is matching by HLA-A and B supertypes, or cross-reactive groups (CREG). (See "Organ sharing in kidney transplantation").

**EXPOSURE TO NONINHERITED HLA ALLELES** — In utero and while nursing, infants are exposed to maternal antigens which the child has not inherited. There is evidence that such exposure may result in some degree of tolerance. One study of 205 patients evaluated the long-term survival of kidney allografts transplanted from siblings with maternal or paternal HLA alleles not inherited by the recipient. Compared to the kidneys donated from siblings with paternal alleles not inherited by the recipient, a higher incidence of survival was significantly observed among the allografts donated from siblings with noninherited maternal alleles at both 5 and 10 years (86 versus 67 percent, and 77 versus 49 percent, respectively). Although many unrecognized factors may be confounding, these results suggest that exposure to donor antigens prior to transplantation may help induce some degree of tolerance.

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**REFERENCES**


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