Racial Equity in Renal Transplantation

The Disparate Impact of HLA-Based Allocation

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KIDNEY transplantation from either a living related or cadaveric donor is optimal treatment for most patients with end-stage renal disease (ESRD).[1] However, due to a critical shortage of organ donors, while more than 23 000 Americans await a suitable cadaveric kidney, fewer than 8000 receive transplants each year.[2,3] Approximately one third of ESRD patients in this country are African American (black), a proportion threefold greater than the representation of this racial group in the general population (12%).[1] Recently, the Inspector General reported that blacks are less likely than whites to receive a transplant, with almost double the waiting time.[4] Currently, cadaveric kidneys are allocated according to a federally mandated system based on quality of HLA matching. This policy is based on evidence that antigenic similarity between donor and recipient may enhance cadaveric graft survival and should be the primary factor influencing distribution.[5] Gjertson and colleagues[6] have proposed that there be even greater emphasis on HLA matching in organ allocation, with all cadaveric kidneys to be placed in a single national pool and distributed to the transplant candidate with the "best" HLA match. In the face of a critical (and growing) shortage of transplantable kidneys, current directives place potential black recipients at a significant disadvantage; extension of HLA-based allocation will magnify racial disparity. We contend that all suitable renal transplant candidates should have equitable access to cadaveric kidneys. To the extent that HLA matching demonstrably improves survival of cadaveric renal allografts, it is an efficient means to effect difficult allocative choices. But, given its documented negative impact on black ESRD patients, the system must be reevaluated to determine whether the cost in equity is truly justified. A recent editorial suggested that "every kidney counts"[7]; we submit, rather, that every patient counts.

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RACIAL DISPARITY IN ESRD AND TRANSPLANTATION

Minority populations in the United States (American Indians, African Americans, and Hispanics) are at increased risk of developing ESRD relative to whites.[8] Blacks are numerically the largest of these minorities and also have the highest incidence of chronic renal failure.[2] Since 1972, Congress, under the auspices of Medicare, has funded ESRD therapy for most Americans, in the form of either long-term dialysis or renal transplantation.[9] A successful kidney transplant imparts several advantages to the recipient, who is more likely to avoid hospitalization, experience a greater sense of well-being, return to the workforce, and, perhaps, live longer than with dialytic therapy.[10-12] Additionally, after the first year, the costs of caring for a transplant recipient are roughly one third of those associated with long-term dialysis.[1] According to a review of the favorable impact of transplantation on the Medicare ESRD program, "Trends in transplantation have not yet had much effect on black beneficiaries ... [who] ... were receiving transplants at only half the rate of white beneficiaries."[1] Indeed, 1989 figures from the US Renal Data System (USRDS) revealed white dialysis patients to be more than twice as likely as black patients to receive a kidney allograft (8.3% vs 3.9%).[2] Kidneys from living, usually related, donors constitute 20% of all transplants.[2] Blacks desiring transplantation are, for poorly defined reasons, less likely than whites to have a suitable living donor and are relatively more dependent on availability of cadaveric kidneys. However, despite their constituting 31% of patients on waiting lists, blacks received only 22% of cadaveric kidney transplants in 1990, with a median waiting time of 13.9 months vs 7.6 months in whites.[4,13] Among American Indians, rates of transplantation are comparable to those for whites; data regarding Hispanic patients are incomplete.[14] Thus, the impact of disparity in transplantation is greatest for African-American patients.

Possible causes of racial disparity in cadaveric transplantation are numerous, to be sure, and have been the subject of a recent review.[14] Black patients in the southeastern United States may be less likely than whites to be referred for transplantation.[15] Although the waiting list at the University of Alabama at Birmingham reflects local ESRD demographics (65% African American), national data support this finding: blacks, despite receiving fewer living related transplants, are relatively underrepresented on cadaveric waiting lists.[4] Moreover, when a cadaveric kidney becomes available, socioeconomic circumstances may limit the ability of potential black recipients to communicate with or travel to the transplant center in a timely fashion.[16] Nevertheless, organ allocation policy, a previously unacknowledged factor, plays a key role in perpetuating disparate racial access to cadav-

eric kidneys and, therefore, to transplantation.

ORGAN ALLOCATION IN THE UNITED STATES

The National Organ Transplantation Act (Public Law 98-507) of 1984 mandated creation of an Organ Procurement and Transplantation Network (OPTN), charged with establishing (1) "a national list of individuals who need organs," (2) a national system "to match organs and individuals included in the list," and (3) "membership criteria and medical criteria for allocating organs."[17] A preexisting entity, the United Network for Organ Sharing (UNOS), was awarded the OPTN contract under the auspices of the Department of Health and Human Services. After 1986, UNOS operated as the OPTN. Under penalty of losing all Medicare funding, the Omnibus Budget Reconciliation Act (Public Law 99-509) of 1986 mandated compliance of organ procurement organizations and transplant centers with UNOS directives.[17] Congress charged UNOS with acquiring and allocating all usable organs "equitably among transplant recipients according to established medical criteria"; accordingly, UNOS developed guidelines affecting kidney allocation at both the local and national levels.

A 1987 UNOS ruling stipulated that if a potential recipient shared all six antigens identified at the HLA-A, HLA-B, and HLA-DR loci with any cadaveric donor, "it is mandatory that the kidney shall be offered for the six antigen patient."[18] Multicenter data had indicated that excellent graft survival could be expected for such recipients; to facilitate outstanding matches, a large donor-recipient pool would be required.[19,20] For the first time, nationwide organ sharing was mandated. Enhanced graft survival for six-antigen–matched recipients (who receive <5% of all cadaveric transplants) was determined to outweigh all other claims on a donated organ and to justify the excess cost and effort required to transport kidneys on a national level.[21] Recently, an identical "six-antigen match" was effectively redefined as phenotypically identical ("zero-antigen mismatch"), extending mandatory sharing to a greater number of harvested kidneys.[22] Graft survival has indeed been excellent (88% at 1 year) in 1004 recipients of mandatorily shared kidneys using both definitions. However, successful engraftment was also achieved in 79% of 22 188 recipients of mismatched kidneys during the same time period.[23,24]

If a donated kidney fails to qualify for mandatory sharing (no six-antigen–matched patient exists), organ allocation occurs at the "local" level, as defined by individual organ procurement organizations. The first attempt to standardize local allocation was the adoption of the "Starzl system" in 1987: "points" were awarded to potential recipients on the basis of quality of HLA match, waiting time, degree of presensitization (presence of anti-HLA antibodies), "medical urgency," and logistic factors such as proximity to the transplant center.[25] The candidate on the local waiting list with the greatest number of points for a particular donated kidney was offered the organ. In 1989, the "Terasaki modification" supplanted the initial algorithm.[26] This revision deleted proximity and urgency as factors and placed greater emphasis on quality of HLA match (Table). Under this system, although other factors (such as age and presensitization) impact the selection process, HLA match is the principal determinant of kidney allocation, with waiting time serving largely as a tiebreaker. For example, a patient with only a single antigen matched could conceivably be given priority for a particular kidney over zero-matched candidates who had waited up to 2 years longer. In the absence of a UNOS-approved alternative plan (termed a variance), all local entities are required to allocate kidneys on this basis.[5]

United Network for Organ Sharing Point System for Kidney Transplant Recipient Selection (1989)

	Points
HLA matching	
No A, B, DR mismatch	10
No B, DR mismatch	7
No A, B mismatch	6
1 B, DR mismatch	3
2 B, DR mismatches	2
3 B, DR mismatches	1
Presensitization	
Panel reactive antibodies ≥80% (negative crossmatch)	4
Waiting time	
Patient with longest waiting time (proportionate fractions of 1 point to patients waiting shorter periods)	1
Each year on waiting list	0.5
Age of children, y	
0-5	2
6-10	1

RACIAL IMPACT OF HLA-BASED ALLOCATION

Despite striking advances in technology, characterization of the major histocompatibility complex (MHC) in humans remains incomplete. It is clear that profound racial differences exist in antigen expression. Blacks have less well-defined HLA antigenic specificities than do whites, particularly at the DR locus.[27,28] Furthermore, HLA antigens are distributed differently among races.[29] For example, at the A locus, HLA-A1 is found in 23% of whites, but only 10% of blacks; conversely, HLA-A23 is much less common in whites (6%) than blacks (22%). Newer histocompatibility approaches, including molecular and epitope matching, by defining more precisely MHC and its products, have demonstrated better correlation of HLA matching with graft survival.[30,31] However, application of these techniques has confirmed the presence of even greater heterogeneity in MHC expression.

When current methodology is considered (ie, serological typing for six A, B, and DR antigens), along with other factors such as linkage disequilibrium, histocompatibility exerts a significant racial impact on organ allocation: the closer the match, the less likely a kidney will cross racial lines.[32,33] Lazda and Blaesing[33] examined the quality of the HLA match between 352 cadaveric donors (86% of whom were white) and a waiting list of potential recipients who were 51% white. Over 70% of potential recipients for whom at least four of six antigens matched were white. These investigators have also noted the rarity of kidneys crossing racial lines with fewer than four mismatched antigens.[34] Emphasis on HLA matching in distribution of cadaveric kidneys disfavors interracial transplantation, a fact acknowledged by proponents of HLA-based allocation.[24]

Accordingly, allocation based on HLA matching promotes racial disparity in access to renal transplantation in the United States. Only 8% of cadaveric kidneys come from black donors; whites donate the overwhelming majority of such organs.[2] Lazda and Blaesing[33] concluded that ". . . using HLA matching to allocate kidneys from a predominantly Caucasian donor population favors the Caucasian recipients and places . . . blacks at a disadvantage." The racial consequences of HLA-based allocation are confirmed by data derived from mandatory sharing of six-antigen–matched kidneys. Of true six-antigen–matched recipients, initial reports documented fewer than 2% as black.[21] Since the incorporation of a phenotypic definition of six-antigen match, this proportion has increased to 7%.[24] At the University of Alabama at Birmingham (with a waiting list that is 65% black) only one of 33 kidneys shipped or received as part of the six-antigen–match program has been for a black patient.[35] Data from UNOS confirm that blacks receive six-antigen–matched kidneys at one-tenth the rate of whites.[36] Hunsicker and Held[37] have estimated that mandatory national sharing of all kidneys with no HLA mismatches would result in a maximum of 8% going to black recipients, with a net overall effect of reducing by 3 percentage points the number of kidneys available for all black candidates. Fur-

ther, at the local level, white patients receive the vast majority of kidney transplants with excellent donor-recipient histocompatibility.[33,34,38] It is not uncommon to see white candidates receive transplants within weeks of placement on the waiting list, solely because they demonstrate common HLA antigen specificities. Indeed, black patients' receiving transplants may actually be facilitated by a small waiting list: a larger list may include more potentially well-matched (ie, white) candidates.

Proponents of HLA-based allocation have suggested further extension of mandatory sharing, with all cadaveric kidneys offered to the candidate with the "best" HLA match on a national basis.[6] They argue that graft survival will be maximized, fewer patients will require retransplantation, and, therefore, more kidneys will be available for those remaining on waiting lists. The potential racial impact of such a policy is not addressed directly, but a "trickle-down" benefit for blacks is suggested as white patients with common HLA antigens receive transplants and are removed from waiting lists. However, in the presence of an organ shortage, with a threefold (and growing) excess of potential recipients, along with racial disparity in MHC expression, there will always be white patients who match the donor population better than black patients. In theory, this discrepancy might be ameliorated by increased organ donation from African Americans.[16,21,33] Blacks may be relatively underrepresented as donors; more African-American donors would mean more well-matched kidneys for black transplant candidates. Although such a solution is attractive, the demographic reality is that, due to overrepresentation of blacks in the ESRD population, there will always be more potential black recipients than donors. Organ donors originate within the general population. In Alabama, blacks make up 24% of the population, 21% of cadaveric donors, yet 65% of those awaiting renal transplants.[39] Nationally, blacks constitute 12% of the population, 8% of donors, but 34% of those with ESRD.[2] To satisfy the demand of African-American candidates for well-matched kidneys, organ donation from blacks must increase by 500%, to a standard far in excess of realistic goals and donation rates within the white community. Although we emphatically support efforts to promote organ donation among blacks (and whites), increased donation by African Americans is not the sole solution to racial disparity in renal transplantation. Moreover, the presumed (though difficult to confirm) lack of participation by black Americans in the organ donation process does not justify policies that enhance access for individual white ESRD patients relative to individual black patients.

EQUITY AND EFFICIENCY IN ORGAN ALLOCATION: RACIAL IMPLICATIONS

As we have noted, the original charge to UNOS was to allocate organs "equitably among transplant recipients according to established medical criteria."[17] Current policies stress the latter portion of this charge by emphasizing quality of HLA match in an attempt to improve transplant outcomes: efficiency is the goal. The Inspector General's report, recognizing disparity in the process, recommends that the Public Health Service, in collaboration with the OPTN, "... distribute donated organs to those patients on a first-come first-served basis, subject to established medical criteria."[4] Equity is thus restated as a primary objective in organ allocation; however, a pure equity-based system, or queue, risks ignoring factors that may have an impact on success rates in transplantation. In both statements, the tension between equity and efficiency centers on the significance of the term "medical criteria." One must then assess whether the benefit of HLA matching in enhancing efficiency is sufficiently great to override equity concerns.[40]

Allocation based on HLA matching is rooted in evidence that antigenic similarity between donor and recipient may enhance graft survival; thus, the most efficient use of a donated organ requires excluding from transplantation those candidates less likely to have a good result (ie, those with a poorer match). Clear correlation between HLA match and outcome is well documented in living related transplantation, where phenotypic matching is a proxy for underlying genetic similarity.[19] However, in cadaveric transplantation, with genetically diverse donors and recipients, benefit from matching is less well defined.[41-44] In the cyclosporine era, outcomes appear to be improved for recipients of extremely well-matched cadaveric transplants: a difference in graft survival of 10 to 14 percentage points at 2 years between best (no mismatches) and worst (completely mismatched) donor-recipient pairs is generally accepted, and confirmed by data from the six-antigen–match program.[44] However, incremental changes in graft survival as one moves from six (completely mismatched) to one mismatch are at most 1 to 3 percentage points and are inconsistently documented.[36,44] Indeed, USRDS data, derived from Medicare records, demonstrate little statistical relationship of HLA match to survival of first allografts at 5 years in the presence of one or more mismatches.[37] For black recipients of first grafts, there is no consistently documented benefit of HLA matching on graft survival.[29,45,46] According to data from the UCLA Transplant Registry, matching may not be a significant prognostic factor for black recipients.[47-49] In a recent review of UNOS data, Cicciarelli and Cho[36] state that "black transplant recipients show little or no matching effect when HLA-A, B, and DR antigens matched." Indeed, subsequent data from the UNOS Registry do not indicate significant improvement in graft survival even for black recipients of phenotypically identical grafts.[24] In retransplantation, which occurs in a more complex immunologic milieu, quality of match may assume greater significance.[37,44,50] Thus, the benefits of allocation based on HLA matching are neither uniform nor unequivocal: its greatest influence occurs in white recipients of phenotypically identical kidneys. Enhanced efficiency for other potential recipients, as well as for the "system," is undocumented.

Moreover, enhanced efficiency is not and cannot be the singular objective of organ allocation. If it were, one could compellingly argue that blacks be completely excluded from cadaveric transplantation. To maximize efficiency, any discount in graft survival may be sufficient for exclusion. An 8- to 19-percentage-point decrement in graft survival for blacks relative to whites is well documented[2,45,47] and quite similar to differences in outcome between extremely well-matched and poorly matched transplants. Allocation of kidneys to whites only (as occurs indirectly in the six-antigen–match program) might therefore enhance graft survival equally as well as hierarchical HLA matching. Efficiency also has a financial context. Gjertson and colleagues[6] suggest that hierarchical HLA-based allocation would potentially save Medicare $6.5 million over 5 years: improved graft survival would more than offset the additional costs derived from matching, preserving, and transporting kidneys nationwide. However, exclusion of blacks from cadaveric transplantation, based on racial differences in graft survival, might save even more money. Extending the analysis of Gjertson and colleagues, with hazard rates derived from Opelz and associates,[51] the estimated 5-year average cost of a transplant (including return to dialysis in the event of graft failure) is $98 300 for a black recipient and $90 700 for a white recipient. Reallocating to whites the approximately 1400 cadaveric kidneys that annually go to black

recipients might save an additional $10.6 million. Obviously, direct racial exclusion to enhance efficiency in either cost or graft survival is morally and ethically unacceptable. The drive for efficiency must be tempered by a more sophisticated policy of accommodation in kidney allocation.

EQUITY AND EFFICIENCY: ACCOMMODATION

If there were no effect of variables such as race and matching on transplant outcomes, tension between equity and efficiency would be eliminated. Recent advances in renal transplantation hold the promise of such nonexclusionary efficiency. Data from several centers have shown graft survival for all recipients of first grafts, regardless of HLA match, to equal those reported in multicenter data for only the best matches.[42] These results have accrued with quadruple immunosuppression, a regimen that combines administration of four potent agents (Minnesota antilymphoblast globulin, cyclosporine, azathioprine, and corticosteroids) in a sequential fashion. At the University of Alabama at Birmingham, this protocol has abrogated racial differences in primary allograft survival over 3 years, despite significantly poorer HLA matching in blacks,[38] a finding confirmed by others.[52] Newer, perhaps more effective and less toxic immunosuppressants (FK506, RS61443, rapamycin, and 15-deoxyspergualin) and monoclonal antibodies (anti–ICAM-1) are on the horizon with the potential to further diminish the impact of HLA matching on graft survival.[53-57]

Despite emphasis on HLA matching to enhance efficiency, current UNOS policies already accommodate equity in some circumstances. A relatively lengthy waiting time for patients of blood type O (universal donor) was thought to reflect the practice of offering kidneys with a better HLA match to an ABO-compatible recipient.[58] As a remedy, UNOS policy was amended to specify that O kidneys be offered only to O recipients (except in the presence of a six-antigen match). Thus, transplant candidates with type O blood are offered equal access to cadaveric kidneys despite the potential of better HLA matches in patients with other ABO types.[22] Furthermore, patients who are highly sensitized to HLA antigens (a situation that limits their ability to accept kidneys from potential donors) receive points to enhance equity, despite the knowledge that presensitization is a risk factor for graft loss.[5] Finally, children, who have poorer graft survival than adults, receive additional points to enhance access to renal transplantation.[59] In each of these situations, some efficiency is sacrificed to achieve greater equity.

Accommodation between the competing goals of racial equity and efficiency, while elusive, is nonetheless attainable. Preference for HLA matching should be given only in proportion to its documented effectiveness in improving graft survival, that is, in extremely well-matched recipients (usually white) and retransplant candidates. Mandatory sharing of phenotypically identical kidneys should continue: its utility is supported by a well-defined dividend in graft survival, and relatively few kidneys (<5%) are removed from the overall cadaveric pool.[23] Kidneys not qualifying for mandatory sharing would continue to be allocated locally; partial matching would be deemphasized, with no points awarded when more than one B or DR antigen is mismatched. If no well-matched candidate is identified for a donated kidney, a policy to enhance allocation to black recipients should be implemented.

A local variance that moves toward more equitable allocation is currently undergoing evaluation in Illinois.[60] Points are awarded only for "excellent" HLA matches, and waiting time is given greater emphasis. While this algorithm enhances black patients' access to kidneys and preserves the efficiency of outstanding matches, its implicit race consciousness does not address the disparity in waiting times between blacks and whites. In fact, it may exacerbate the problem: prolonged time on the list is required for black patients to accumulate enough "points" to offset the advantage to whites of better matching. Thus, although data are not yet available, the Illinois variance avoids specific reference to race but may perpetuate inequity in waiting times.

An alternative proposal might recognize more explicitly the racial implications of HLA-based allocation and award points to blacks without requiring excessive waiting time. "Race-conscious points" could be used to compensate for points accumulated by whites on the basis of HLA matching. Such a plan offers reduced racial discrepancy in both frequency of transplantation and waiting times, with maintained efficiency for well-matched recipients. Its principal liability is explicit race consciousness, a factor that may conflict with other social norms: race, a concept based primarily on skin color rather than physiological difference, must be defined.[61] Realizing the arbitrary nature of any definition, we would propose a simple one: allow transplant candidates to define their own racial origin, much as is currently done in collecting USRDS and UNOS data.[2,44] Thoughtful dialogue is necessary to further refine such a radical solution. Nevertheless, an approach that openly confronts racial differences may be required, at least temporarily, if equity is to be achieved.

CONCLUSION

The equitable and efficient distribution of limited resources, such as cadaveric kidneys, requires careful evaluation of all the effects of allocative choices that are made. In this essay, we have focused, perhaps simplistically, on the racial impact of allocation policies: clearly, race is not the sole issue impacting organ allocation. However, HLA-based allocation is equally simplistic in the assumption that universal benefit will result from better matching. The truth is that some will benefit, and others will not. Disproportionate representation of African Americans in the ESRD population dictates that racial considerations cannot be ignored in the distribution of cadaveric kidneys in the United States. Efforts to increase black donation are to be encouraged but will not eliminate disparity. If racial equity in renal transplantation is to be achieved, alternative allocation strategies must be formulated that forthrightly address the interests of all potential recipients.

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