ETHNIC AND RACIAL DIVERSITY IN TRANSPLANTATION: DOES EVERYONE BENEFIT EQUALLY?*

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ABSTRACT

As in other areas of medicine, ethnic and racial disparities are evident in renal transplantation. Key cultural factors affecting transplant outcomes may include the patient's health beliefs and practices, socioeconomic status, adherence to therapy, previous experiences with discrimination, lack of trust in healthcare providers, provider bias, and linguistic incompetency. Policies, structures, and resources devoted to increasing cultural and linguistic competency are needed. A range of cultural and socioeconomic factors have contributed to an excess prevalence of hypertension, diabetes, obesity, and renal disease in African American and Hispanic populations. Genetic factors are less important. Unfortunately, access to transplantation for minority patients is lower than for Caucasians. Lack of health insurance contributes to both increased renal disease and decreased access to advanced care. After transplantation, African American patients tend to have worse outcomes.

Genetic factors such as polymorphisms that impact immunosuppressive drug metabolism may contribute to some of this racial variation. Inherited differences in pharmacodynamics or immunity may also account for some of the poor outcomes. However, as demonstrated in recent analyses of immune risk and maintenance immunosuppression, poor outcomes among African Americans still seems to be linked to acquired characteristics such as lack of insurance, preexisting time on dialysis, or compromised adherence to maintenance immunosuppression related to a variety of complex factors. (Adv Stud Med. 2007;7(9):268-274)

The racial and ethnic disparities prevalent throughout healthcare and many other sectors of American life extend, not surprisingly, to the field of solid organ transplantation. In the United States, ethnic minorities suffer disproportionately from kidney disease (eg, African Americans have a 4.2-fold higher rate of end-stage renal disease [ESRD] than their white counterparts) and minority populations are also known to be more adversely affected by limited preventive medical care, lack of counseling regarding transplant options, and delays in organ referrals. As reviewed in this article, the complex issues of diversity in renal transplantation can be illuminated from the varying perspectives of cultural and linguistic competency, access to care, differential treatment, and long-term outcomes.

CULTURAL AND LINGUISTIC COMPETENCE:
Racial and ethnic disparities in healthcare, including in the field of solid organ transplantation, occur in the context of broader historic and contemporary social and economic inequality. To understand the nature of this unequal care and outcomes, an array of overlapping cultural factors can be considered (Figure 1).

The literature cites race, gender, ethnicity, religiosity, and age (both actual and perceived) as contributing factors in disparity in transplantation. Although more study is needed to explain how these factors operate and interact, the evidence suggests that these core cultural traits are linked with disparities in transplantation just as they are in other areas of surgery.

Key patient attributes impacting transplant outcomes may include health beliefs and practices that impact decision making, the correlation between socioeconomic status and adherence, previous experiences with discrimination in care, and a deep lack of trust of healthcare providers and institutions.

Other cultural influences may impinge on these individual factors to create further disparity. At the family level, for example, African Americans are less likely to serve as living donors or to donate the organs of their loved ones due to an overall mistrust of the healthcare system and a fear that organs would be used for non-African American patients. Provider bias cannot be ruled out as a cause of racial differences in who is identified as a potential transplant candidate and who languishes on the wait list. Further, on a broader level, there is a lingering perception in segments of the African American community that the system won’t save their lives if they are seriously ill or injured and that those who are poor or of racially ethnically diverse backgrounds will not ultimately benefit from the transplantation system.

Given the likelihood that multiple cultural factors negatively influence transplantation outcomes for African Americans and other racial/ethnic groups, it seems clear that cultural competency must be encouraged at both the organizational and the individual level. There are 5 essential elements that healthcare organizations must consider in achieving cultural competence. These elements include learning to value diversity; developing the ability for self-reflection and conducting an honest cultural self-assessment; managing the dynamics of difference; acquiring and institutionalizing cultural knowledge (ie, so it is not reliant on the presence of any one employee); and being able to implement change in organizational values, policies, structures, and services to respond to diverse patient populations. For the individual, the first steps typically involve an acknowledgement of cultural differences and an understanding of one’s own culture, including the culture of medicine, perhaps beginning with some form of formal self-assessment. Cultural competence is a developmental process that moves beyond awareness to the acquisition of knowledge and skill sets that enable providers to work effectively in cross-cultural encounters with diverse patient populations and communities.

Linguistic competency is also required to ensure that information about renal transplantation is communicated in a manner easily understood by diverse patient populations. Perhaps one of the most blatant examples of culturally destructive practices in healthcare is the continued widespread use of children as interpreters for adult family members. Another area that merits mention is the intersection between health literacy and the complex legal language used in informed consent forms that may contribute to persistent inequalities in renal transplantation. Note that, unlike cultural competency, linguistic competency or language access is actually mandated by federal law (Title VI). Many groups state that an organization’s capacity to communicate effectively must also reach beyond those populations with limited English profi-
efficiency to include those with low literacy, low health literacy, and disabilities.6

Achieving cultural and linguistic competence in transplantation is a long-term goal that will require an integration of community engagement; provider awareness, knowledge, and skills; organizational self-assessment; a robust research agenda in partnership with diverse patients and communities; and credible voices to deliver messages that transplantation is an accepted practice to address racial and ethnic disparities within this nation’s diverse communities (Figure 2).6

ACCESS TO CARE

Improving access to kidney transplantation remains a persistent challenge for the transplant community. As the underlying burden of both chronic and ESRD has continued to grow over the past decade,2,22 the size of the transplantation wait list has increased by 61% and the median wait time to transplantation has also lengthened considerably (Figure 3).2 Although the supply-demand imbalance for donated organs is felt by all patients with severe kidney disease, poor access to transplantation for minority populations is an issue that goes far beyond the ongoing donor shortage.23-25 In particular, the broader issues of access in these minority populations involve increased underlying renal risk and ongoing disparities in medical care—both of which are driven by complex and often difficult-to-measure sociocultural factors.

African American and Hispanic patients have especially high prevalences of renal disease, an excess burden that is likely related to the higher rates of hypertension, diabetes, and obesity seen in these minority populations (Figure 4).26 When adjusted for age, the relative race-related differences in the prevalence of these risk factors are even greater.27,28 Likely contributors to these underlying risk factors include poverty, low birth weight, poor nutrition in childhood, and a range of other historic, cultural, and socioeconomic factors that influence lifestyle, health, and access to healthcare.29,30 Genetics appear to play a very limited role in the elevated cardiovascular and renal risk of minority patients.29

Despite the clearly elevated need for the surgical

Adapted with permission from US Renal Data System, USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, Md: National Institutes of Health, National Institute of Diabetes, and Digestive and Kidney Diseases; 2006. (The data reported here have been supplied by the United States Renal Data System [USRDS]. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.)
option in minority patients, their access to potentially life-saving transplantation is lower than seen in Caucasians. This is evidenced by lower rates in several key categories—referral for evaluation, placement on the wait list, and actual receipt of a transplant (Figure 5). In African American patients, the disparities such as time spent on wait list are projected to continue (Figure 3).

Lack of health insurance likely contributes both to increased renal disease and to decreased access to advanced care, including transplantation. Clinicians are well aware of the 47 million Americans (90% of whom have jobs) without insurance and the other 20 to 40 million who are underinsured. Overall, according to the 2004 National Health Interview Survey, 30% of Hispanics and nearly 15% of African Americans in the United States are uninsured. Of all those with ESRD, 35% of Hispanics and 20% of African Americans are uninsured compared to 12% of white patients. These patients without adequate insurance are not only more likely to have chronic conditions that exclude them as donors, they are also more likely to lack the coverage needed to pay for complex services such as transplantation.

There is no known genetic reason for the epidemic of chronic kidney disease or for the episodic access to transplantation care now seen in populations of minority patients. Transplant specialists need to ask themselves why disparities in transplantation care still exist and then take steps to ensure that all patients get the full range of preventive, chronic, and acute care that will eventually equalize access to care and clinical outcomes.

OUTCOMES: WHAT HAPPENS AFTER TRANSPLANTATION?

Kidney transplantation reduces mortality in all racial and ethnic groups compared with dialysis, but registry data consistently show that African American patients have worse outcomes after kidney transplantation versus Caucasian patients. One recent white paper reported 3-year graft survival rates of 73.9% and 81.6% in African American and Caucasian patients, respectively. In another study, African American patients with all 6 human leukocyte antigen (HLA) matches had 4-year allograft survival rates identical to those seen in Caucasian patients with no HLA matches. Although some have suggested that modern immunosuppressive regimens have diminished race-related differences in outcomes, most large studies involving immunosuppression with newer agents, such as mycophenolate mofetil (MMF), still indicate that African American patients lag behind Caucasians in outcomes.

What accounts for lower allograft survival in African American patients? Some evidence points to genetic factors involving immunologic or pharmacologic/pharmacogenetic traits. For example, in one study of HLA-identical recipients, African American patients still had higher rates of acute (in-hospital) rejection, strongly suggesting genetic factors rather than socioeconomic factors such as noncompliance.
with immunosuppression.37 However, other evidence such as a study showing equivalent 5-year outcomes in African Europeans and Caucasians points to environmental influences.38

Inherited pharmacologic factors may account for some of the disparities. Most obviously, studies with calcineurin inhibitors (CNIs) confirm what many clinicians witness in their daily practice—African American patients need higher doses of CNIs to achieve equivalent exposures and clinical outcomes.39,40 The microemulsion formulation of cyclosporine has narrowed the gap in CNI bioavailability, but African American patients still require doses approximately 10% to 20% higher than Caucasians to achieve equivalent blood levels.41

Gene polymorphisms affecting drug transport, metabolism, and elimination of drugs may explain some of this pharmacologic variability. Patients who express the CYP3A5*1 isoform require more tacrolimus to achieve therapeutic drug levels, and 50% of African Americans express this variant versus just 10% to 30% of Caucasians.42 Similarly, the membrane pump P-glycoprotein encoded for by ABCB1 affects drug absorption and drug distribution in tissues. Eighty-four percent of African Americans are “high-pumpers” (in comparison with 22% of Caucasians) and absorb immunosuppressive drugs suboptimally.43

Pharmacodynamic rather than pharmacologic variables may explain other racial variations in outcomes reported in immunosuppression trials. For example, the sirolimus registration data showed that African American patients required a 5-mg daily dose to achieve the same reduction in acute rejection (versus azathioprine) as Caucasian patients achieved with a 2-mg daily dose, despite evidence of essentially equivalent mean trough levels with identical doses.44 Similarly, only African American patients receiving 3 g of MMF daily achieved a statistically significant reduction in biopsy-proven rejection or treatment failure, whereas Caucasian patients achieved this level of reduction with 2 g of MMF daily.45

Immune factors, such as HLA variants, Duffy blood types, and increased immune responsiveness, have also been proposed as genetic reasons for lower allograft survival rates in African American patients. Studies are ongoing to evaluate the genetic and clinical correlates of such factors.46 Two recent studies help illustrate the impact of immune factors on transplantation outcomes in African American patients.

We used a pretransplantation enzyme-linked immunosorbent spot (ELISPOT) assay to measure the frequency of peripheral T cells that express interferon gamma.47 Because longer time on dialysis is strongly associated with higher risk of rejection,48 we evaluated the impacts of both time on dialysis and ethnicity on ELISPOT results in a group of 100 kidney recipients. As expected, acute rejection rates were significantly higher in ELISPOT-positive patients (38%) versus ELISPOT-negative patients (14%; \( P = .008 \)), and those patients who had spent more time on dialysis were ELISPOT positive significantly more often than those of “lower hemodialysis vintage.” The most relevant finding in this study was that the higher rate of ELISPOT positivity seen in African American patients disappeared after controlling for time on dialysis. This suggests that any heightened immune responsiveness in African American patients may in fact be acquired rather than inherited, and that clinicians might best circumvent high rates of rejection in African American patients by transplanting them sooner.

Preliminary unpublished results from an ongoing study of sirolimus combined with a CNI in 347 African American patients have shown low rates of acute rejection (15.3%) and graft loss (5.2%) at 12 months. Although these results are encouraging and suggest that a potent immunosuppressive maintenance therapy can limit rejection in African American patients, longer term outcomes are required. Our own study of maintenance immunosuppression had posted similarly encouraging outcomes at the 2-year mark only to see dismal outcomes in African American patients at 4 years.49,50 The likely cause of the long-term failure was nonadherence, which as noted by others may be related to lack of insurance or other complex socioeconomic factors rather than simple forgetfulness or lack of education.51-53

CONCLUSIONS

The lower rates of allograft survival still seen in African American patients are due to a variety of factors that are not easily separated. Although we must continue to study the biologic basis of outcome differences in diverse ethnic populations (eg, the genetics of immune responses and pharmacogenetic profiles), researchers and clinicians alike must not lose sight of the fact that socioeconomic variables and ingrained
disparities in the delivery of transplantation care (eg, delayed referrals and prolonged waiting times) continue to negatively influence outcomes.1

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