

Rationing Scarce Cadaver Organs: A Medical Responsibility?

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Transplantation is a specialty that raises the prickliest questions because it saves lives, prolongs good-quality life in the terminally ill, is extremely costly, and invokes ethical and social issues of administering the public resource of donated organs. Worldwide, there is a sorrowful state of organ shortage, with the result that patients are suffering while waiting for unavailable new kidneys, livers, pancreases, hearts and lungs.

The paper by Mor et al. in this issue [1] reports on the efforts made by the Israel Transplant Center to shorten the inordinately long time that patients in end-stage renal failure have to wait to receive a transplant (the mean time is 3 years 8 months). The Spanish model for organ donation and the use of marginal donors were applied to expand the national donor pool. Spain currently has 139 hospital coordinating teams, one in each hospital. These transplant coordinators are involved in donation and organ procurement processes and are accountable for performance [2]. This policy led to a shift, in Israel, toward elderly donors (40% over 50 years old) with cerebrovascular accident (47%). Kidneys from donors over 50 years were at significant increased risk for delayed function and for primary non-function (38%) as compared with donors under 50 (19%). Age-matching policy (i.e., the allocation of an old kidney to an old patient) was an additional factor for poor outcome. The authors suggest that the cold ischemia delay be shortened and that stable first-graft recipients be selected.

Donor age and delayed graft function in rejection-free patients are indeed risk factors for allograft failure. The senescent kidney is more vulnerable to ischemic and reperfusion injuries since nephron mass is reduced in the elderly. Therefore, every effort should be made to reduce ischemia stress. Also, following the dilemma to exclude organs, the use of two marginal kidneys in a single recipient might be an option [3].

However the second suggestion, selection of stable patients, may not be applicable since patients are not ranked by their health status. Factors like "non-stability" or "severity" are not quantifiable and cannot be used in the policy making of allocation.

Considering an outcome-based approach to rationing organs, the credible responsibility for the decision as to who shall get the next organ has fallen to the medical

cadres. Transplant physicians and immunologists have established the rules of kidney allocation with factors such as recipient age, waiting time, HLA matching and sensitization degree — presuming that these factors are predictive of outcome [4]. This assumption is at the center of a debate that has, in my opinion, gone beyond the medical barriers.

Major histocompatibility complex antigens were identified partly because of the powerful graft rejection they cause. Identification of the MHC antigens of donors and recipients is performed in tissue typing laboratories using several different serological methods and, more recently, several different molecular biology approaches. The six HLA antigens used in transplantation represent a small part of the MHC we know about. Thus we should keep in mind that the information available is incomplete and imprecise. It is generally accepted from data analysis of large transplant registries that better antigen matching provides a better kidney graft survival. Should we use then the level of HLA matching to determine the distribution of organs? The benefits of the effort to match MHC antigens means that for kidneys there is about a 10% better 1-year graft survival for six antigens-matched organs compared to those distributed randomly. The disadvantages include the high costs, problems associated with longer ischemic times, and the inequities for patients forced to wait longer for an organ.

During the debate over the relative importance of HLA matching and graft survival, immunosuppressive therapy has become more specific and more successful in preventing and reversing allograft rejection; thus the need to include MHC matching as a rationing factor should be reconsidered.

In the article by Tambur and Klein, also in this issue of *IMAJ* [5], the authors assume that in order to reduce cold ischemia time, a patient with 0% anti-HLA antibody can proceed to transplantation without waiting for prospective crossmatch results. The restriction is that the assignment of 0% antibody is made by flow panel reactive antibody methodology. For sensitized patients, a fluorescence-activated cell sorter crossmatch has become the standard method, even if the logistics are not trivial.

MHC = major histocompatibility complex

The crossmatch determines whether recipients have pre-formed serum antibodies reactive with donor cell antigens. Kidney transplants are frequently undertaken when there is a negative crossmatch and poor antigen matching, but they are never performed if there is a positive crossmatch even with good antigen matching. As with any assay, there are several different techniques, therefore each laboratory has to determine its own thresholds for judging what is a positive crossmatch. Among the variations used to provide a higher degree of accuracy are varying the type of cells, sorting them by FACS analysis, and reducing IgM isotype. Most laboratories consider the antihuman antibody-augmented detectable complement-mediated lysis of T cells to be positive, even at very low dilutions. That standard is very effective in preventing hyperacute rejection. But more stringent criteria, such as rejecting weakly B cell-positive crossmatch, might improve long-term allograft results. It will also certainly exclude some patients carrying pre-formed anti-class II antibodies with no clinical significance.

Sensitization that refers to the range of HLA antigens to which pre-formed antibodies are detectable is a crucial issue because this immunologic status is a penalty for patients awaiting transplantation. Highly sensitized patients with so-called 100% panel reactive antibodies are not reactive to the entire HLA system; rather, most have a few different antibodies that are broadly cross-reactive with many different HLA antigens, the so-called public epitopes (cross-reactive epitope genes). An accurate MHC determination may be useful to search for donors expressing "safe" HLA phenotypes for sensitized patients.

With so many variables involved, some have argued that tissue typing laboratories should focus their efforts not on achieving better antigen matching, but rather on finding crossmatch negative donors for sensitized patients. Should we aim for the best predictive outcome or an equal chance for everybody? Should this dilemma be solely a medical issue?

Allograft survival outcomes are multifactorial. Results may be influenced by pre-formed anti-HLA antibodies or HLA matching; but to clinicians, it is the optimization of the patient status, the quality and management of the donor, the reduction of operative morbidity, and the

ongoing close recipient care, that constitute the major determinants of outcome.

In long-term follow-up of transplant patients, we can observe severe conditions due to cardiovascular, immunodeficiency, bone and neoplastic diseases. However, the incidence and severity of these medical endpoints cannot be predicted and do not justify rationing. Also, there may be significant race and sex differences in certain outcomes; would someone assume in that case that there is moral justification to base rationing on the predictability of outcomes? Thus, if there are no strong genetic or outcome-based medical arguments to influence the decision on organ allocation, the only crucial impact of the medical profession on the management of scarce public resources is to exclude those few with absolute contraindications to transplantation.

Addressing the issue of the rules of rationing in a shortage, we need to examine the moral philosophy underlying a rationing policy, in the light of distributive justice and equity. There is little justification that the decision on such a policy should be made solely by physicians. To answer the question of who shall live and who not, the community has to convene selected members who will represent and defend the values of the whole society. I see no other way.

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Originally, the Africans had the land and the English had the Bible. Then the missionaries came to Africa and got the Africans to close their eyes and fold their hands and pray. And when they opened their eyes, the English had the land and the Africans had the Bible.

Jomo Kenyatta, President of Kenya 1889-1978

FACS = fluorescence-activated cell sorter