Renal transplantation

An analysis of logistical and medical factors affecting cadaver organ availability[1]

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The National Organ Transplant Act (PL98-507) was enacted in 1984 to support the continued development of a comprehensive procurement and distribution network in the United States for transplantable organs and tissues as well as a registry for potential recipients. Demand for one organ, the kidney, has increased dramatically for a number of desirable reasons: More patients have been accepted for transplantation, age limits for transplantation have been extended, results have improved, and there are more transplantation centers doing more transplants. Undesirable factors have also increased the demand: There has been no major breakthrough in treatment of the renal diseases that most frequently progress to end-stage failure, and graft rejection continues to be a problem. On the other hand, the supply of cadaver kidneys has decreased: Fortunately, the number of fatal motor vehicle accidents has fallen because of the lowered highway speed limit and seat belt use, but, unfortunately, public misconceptions about transplants, lawsuits against physicians participating in cadaver organ retrieval, and gaps in professional understanding have also decreased the supply. Although rejection can be treated with immunosuppression after transplantation, histocompatibility matching of donor and recipient before transplantation has significantly increased graft survival. The national initiative may provide the critical mass necessary to correct some of the misconceptions and lingering problems that frustrate the optimal use and success of human organ transplants.

Index terms: Histocompatibility testing · Transplantation

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On October 19, 1984, President Reagan signed the National Organ Transplant Act (PL 98-507) into law. The legislation is intended to provide, in an equitable and

intelligent way, an adequate number of organs and tissues for all suitable transplant candidates in the United States. It establishes a task force on organ procurement and a broad range of issues related to the medical, legal, ethical, social, and economic aspects of transplantation. Furthermore, it provides assistance for organ procurement agencies, directs that a comprehensive network for organ procurement and transplantation as well as a scientific registry be established, and prohibits the purchase and sale of human organs. The impetus for this legislation arose because of the terrible discrepancy between the supply of and demand for cadaver organs. The need for kidneys has been increasing for years, but it is the current surge in the need for hearts and livers that is truly a matter of life and death. Candidates for these organs have no well-established, alternative life support system as kidney patients do with dialysis. The dramatic appeals from parents to national organizations and even to the White House generated the critical mass of popular and political support necessary to develop such legislation.[1]

Desirable factors increasing the demand for cadaver kidneys

Although the demand for cadaveric kidneys far exceeds the supply, some factors contributing to the increased demand are desirable. More patients, especially diabetics, have been accepted on chronic dialysis programs, expanding the number of potential transplant candidates.[2-4] Data from the Department of Health and Human Services indicate that the number of end-stage renal disease patients has increased from 16,000 at the outset of the federally funded program in 1973 to about 57,000 in 1980 and about 80,000 in 1984.[5,6] Not only has the number of transplant candidates increased, based on traditional acceptance criteria, but there has also been a definite trend to extend the age limits for transplantation beyond 60 years because of the encouraging results with transplant patients over 50.[7] The improved results of transplantation in general have attracted a larger number of transplant candidates.[8,9] The International Transplantation Study, using data from 211 transplant centers throughout the world and including more than 7,000 cadaveric transplants, has shown that, in first-cadaver transplant recipients, the overall one-year success rates now are approximately 67%, and there is a group of 30 centers that have one-year graft success rates averaging 80%.[10] In addition to the improving results, the sheer volume increase of transplantation at many centers has stimulated more patients to seek this option.[11,12] About 1975 there were just two centers performing more than 100 transplants a year, whereas there are now at least 10, with two doing more than 200.[4,13] There were also at least 40 transplant centers performing more than 50 transplants per year, contributing to the total of some 6,968 renal transplants in 1984. About 10 centers in the United States have passed or are about to pass the 1,000 kidney transplant milestone. Thus, the increased activity with improved results, the liberalized criteria for accepting candidates, and the expanding number of patients, particularly diabetics, on chronic dialysis have all combined to accentuate the demand for cadaveric kidneys. Certainly no one would want to dampen the justifiable enthusiasm of patients for this treatment or to return to unnecessarily restrictive criteria for transplant candidates. Consequently, none of these factors can really be reduced.

Undesirable factors increasing the demand for cadaver kidneys

However, there are some undesirable factors contributing to the increased demand for cadaveric kidneys. The first of these is the unfortunate fact that, with the possible exception of dietary protein restriction,[14] there has been no extraordinary breakthrough in the prevention or early reversal of the renal diseases that most frequently progress to end-stage failure. Since about half of all the renal diseases that do so are generated by immunopathologic mechanisms, the exciting advances in immunology, immunogenetics, and molecular biology may soon make impressive contributions to stemming the relentless deterioration typical of these renal diseases.[15-18]

A second undesirable factor, graft failure, is one that, surprisingly, can be ameliorated simply by education and perhaps changes in attitudes and philosophy. We know that rejection is still the primary cause of renal allograft failure, and minimizing the chances of rejection at the very outset would reduce the frequency of rejections leading to allograft loss and the need for repeated high doses of various immunosuppressants. In fact, the whole process is the immunologic coun-

terpart of the political domino theory in which gross histoincompatibility between the donor and recipient leads to severe rejections; severe rejections, in turn, lead to the increased use of immunosupressants and graft failure in many cases, as well as sensitization for many of those who need another transplant; and it is immunosuppression that ultimately increases patient morbidity and mortality. Fundamentally, the long-term effects of histocompatibility favor both the patient and the allograft, whereas the long-term effects of immunosuppression create continuing risks for both the patient and the graft.

Is there evidence to show that donor-recipient histocompatibility can significantly change this series of unfavorable events and improve graft survival? If there is, then with other factors unchanged, when grafts last longer, waiting lists will be shorter.

The questions to be asked are straightforward: First, what is the effect of HLA histocompatibility matching on short-term survival of cadaver renal allografts; second, what is the effect of HLA matching on long-term graft survival; third, what is the effect of matching on the ability to decrease or stop prednisone after transplantation; and, fourth, what is the effect of matching on the costs of treating patients with end-stage renal failure?

Histocompatibility and short-term kidney allograft survival

The answer to the first question posed above is unfolding dramatically from the International Collaborative Renal Transplant Study organized by Dr. Gerhard Opelz in Heidelberg, Germany.[10] This study has collected prospective information on renal transplants from 211 centers in 31 countries. Through June of 1984, there were 14,570 transplants reported since the study began in January of 1982. About three-fourths of these transplants were from cadavers, and more than 7,000 have been analyzed.

In this study, the effect of matching for HLA-A, B, and DR antigens is clear: Sharing both A, both B, and both DR antigens, for a total of six, yielded an allograft survival of 85% at six months compared with the other extreme of 65% survival when no antigens were shared. At one year, only 58% of grafts survived for those with all of the A, B, and DR antigens mismatched, whereas 78% of the grafts survived in the group of patients with no mismatches. The major portion of the matching effect was contributed by the combination of B and DR antigens; sharing both B and both DR antigens, for a total of four, gave one-year graft survivals of 83% compared with 58% when none of the B or DR antigens was matched.

There has been concern whether matching was effective only in European centers. However, the data clearly show that the effect of mismatching B and DR antigens in first cadaveric graft recipients was even more apparent in the North American component of this study than in the group as a whole, with 82% graft survival for those with no B or DR antigens mismatched compared with just 55% when all four of these antigens were mismatched. Simply avoiding mismatching for the A and B series of antigens significantly improved survival for the North American recipients of first cadaver grafts; with no mismatches for these antigens, one-year graft survival was 76% compared with 58% when all four of these antigens were mismatched. Even with transfusions, HLA matching for the B and DR antigens improved allograft success with 75% one-year graft survivals when all four B and DR antigens were matched compared with 52% when they were mismatched.

But the most important and timely question is whether HLA matching has any significant effect when cyclosporine is used as an immunosuppressant. With cyclosporine, avoiding any mismatching for just DR antigens improved allograft survival from 72% to 82% at one year.[19] But the most dramatic effect of histocompatibility matching with cyclosporine use was noted once again with the combination of B and DR matching: 86% ± 3% of 161 allografts with no mismatches survived to one year compared with 67% ± 4% of 181 grafts with all four of these antigens mismatched ($P < 0.001$). Most of the advantage gained by using cyclosporine was lost by using poor matches.

Some centers made a special effort to use DR matching before cyclosporine was available or when it was not used. Lucas et al. at the University of Kentucky reported that, with no DR mismatches, one-year survival of cadaver grafts was 84% in 43 recipients of a first graft and 80% in 10 recipients of second transplants.[20] Similarly, Vanderwerf in Phoenix reported one-year graft survival of 80% in 78 patients by avoiding DR mismatching compared with 55% in 38 patients

with one or two DR mismatches (B. Vanderwerf, personal communication). The problem here is that without exchange of cadaver kidneys among transplant centers many excellent matches will be excluded and the additive effects of matching and cyclosporine will be missed.

Histocompatibility and long-term kidney allograft survival

Nobel laureate Jean Dausset addressed the second question: what is the effect of HLA matching on long-term graft survival? He reported that in 2,069 first cadaver-allograft recipients the eight-year graft survival was nearly double in recipients who were matched for two, or three to four A- and B-series antigens (34% and 38%, respectively) compared with those matched for zero or one of these antigens (20% survival) ($P < 0.001$).[21] Further evidence of this long-term effect of matching was recently reported by Sanfilippo et al. for the Southeastern Organ Procurement Foundation (SEOPF); their study showed that, four years after cadaver allografting, patients with no A and B matches had just 18% graft survival compared with 44% for those with four antigens matched.[22]

Histocompatibility and steroid dosage

A preliminary answer to the third question is again offered by the SEOPF study: in both first transplants and repeat transplants, significantly less prednisone and methylprednisolone was used in better-matched recipients than in the poorer-matched ones.[22] For example, the first-year cumulative prednisone dose decreased from 11,206 mg in the poorly matched first cadaver-allograft recipients to 10,572 mg in the better-matched ones ($P = 0.04$), and the methylprednisolone dose decreased from an average of 5,548 mg to 3,634 mg ($P = 0.0001$). Similar significant differences were apparent in repeat transplants. Lange et al. took another approach to the steroid question. They reported that, in patients who left the hospital with functioning cadaver allografts, gradual attempts to stop prednisone were successful in 12 patients who had an average of just 0.58 incompatible antigens, temporarily successful in another 24 patients with mean mismatched antigen levels of 0.83, and impossible in 66 patients with the highest average level of incompatible antigens at 1.29.[23]

These data show that histocompatibility matching at the outset could increase short-term graft survivals, increase long-term survivals, support decreased immunosuppressant dosage and consequent morbidity and mortality, and probably decrease the number of highly sensitized recipients awaiting a repeat transplant.[24] Is it possible that *an ounce of histocompatiblity is worth a pound of cyclosporine?*

We should be looking beyond 1- to 2-year allograft survivals and use a strategy in transplantation, whenever feasible, that will permit genetics to make its contribution to long-term graft survival, allow the use of lower doses of immunosuppressants, and afford a better opportunity for retransplantation to those patients whose first allografts fail. This is not a challenge to cyclosporine being a powerful immunosuppressant. It is simply a statement that the most intelligent, economical, and safe way to use it, like any other drug, is to set the conditions in such a way that the least amount of the drug can have the optimal effect. Greater histocompatibility plus lower cyclosporine dosages may offer the patients the best of both worlds.

Histocompatibility and costs of end-stage renal disease

The cost saved by using histocompatibility matching in cadaver transplants can be approximated as follows: About three-quarters of the 6,968 kidney transplants done in 1984 were from cadaver donors, or about 5,226 transplants. Estimates of the additional costs incurred for each graft failure are $15,000.[66] If there is an overall one-year cadaver graft success rate of 70% from all types of centers, there is a failure rate of 30% that includes 22% simple graft failure and 8% death with graft failure. Simple graft failure incurs an extra cost of approximately $15,000, whereas death as a cause of graft failure costs about $25,000. Consequently, the total cost of failure is $27,697,800 [(0.22 × 5,226 × 15,000) + (0.08 × 5,226 × 25,000)]. To round off, 28 million dollars for a 30% failure rate (at current levels of transplantation and recent charges) means that for every 1% improvement in success rate, nearly $1,000,000 can be saved!

Because rejection and the complications of rejection therapy are the overwhelming causes of graft and patient loss, histocompatibility is an important consideration. Matching for the HLA histocompatibility antigens even without cyclo-

sporine can increase success rates by as much as 17%, and, with cyclosporine, as much as 19%, saving 17 to 19 million dollars from the worst to the best match. Since not all the patients would be well matched, even if two-thirds of that objective could be attained, it would save about 12 million dollars in just the first year at current levels of transplantation and more than that as more transplants are done.

Moreover, at four to eight years after transplantation, poor matching cuts the success rates in half from the best to the worst matches. Therefore, whatever costs are incurred for later graft or patient loss from rejection or its treatment complications, the proportion of those costs will be doubled for the poorly matched patients.

Other costly disadvantages of rejecting a graft are the earlier reinstitution of chronic dialysis (about $21,000 composite per year for dialysis) and the longer wait for the next kidney while continuing on dialysis—both more likely in poorly matched recipients. Effective drug dosages and, therefore, their cost, particularly for cyclosporine, can be expected to be lower in the well-matched recipients. Moreover, histocompatibility testing is a one-time charge, whereas immunosuppression is a continuing nonfixed expense.

Factors decreasing the supply of cadaver kidneys

Although there is at least one desirable basis for a decrease in cadaver organs, the lower number of fatal motor vehicle accidents with the 55 mph speed limit and the use of seat belts, there are more undesirable reasons why the number of cadaveric organs is inadequate to meet the needs of patients with end-stage renal disease. At times, books and movies depicting murderous schemes to procure organs for sale create subtle waves of public apprehension that are reflected in noticeable downward trends in organ donation.[25] Although they seem mostly a thing of the past, lawsuits against physicians harvesting and transplanting cadaveric organs from brain-dead donors have created painful episodes in circumstances that require the utmost professional sensitivity. In addition, gaps in public education have caused confusion and uncertainty about donating organs. For example, some still think that there is a large data bank somewhere with all of the potential donors listed for use by an individual in need of an organ.[26] The effectiveness of signing organ donor cards, whether separate from or on drivers' licenses, is still being debated.[27] There are gaps in professional education, with uncertainties arising from time to time about the definition of death and the means of initiating donor procurement efforts.[28] Many professional groups are addressing these problems effectively. Techniques for harvesting and preserving donor organs as well as the typing and crossmatching recipients are receiving continued review and quality assurance.[29,30]

But there are other areas in which information already available is poorly understood. The result is that transplantation resources are not used to their best advantage, kidneys are not exchanged widely enough, and most important, patients must wait longer for transplants.

One such bit of misinformation concerns the interpretation of the panel reactive antibody (PRA). A high PRA value is often used to identify patients as being hard-to-transplant. The PRA is the number of positive cytotoxic tests divided by the total number of tests done, using a panel of donor lymphocytes. However, the PRA calculation often provides misleading information about the population frequency of the unacceptable donor antigen(s) because: (1) its value is affected by the composition of the lymphocyte panel, which may not accurately reflect the frequency of the antigens in the donor population; (2) it provides no information about the specificity of the antibody (e.g., whether it is an anti-HLA-A2); and (3) it incorporates no information about the other major transplantation antigen system, namely ABO, the frequency of which should also be factored into any probability calculation for transplantation. In contrast, the cumulative probability (P_c) of transplantation is based on the population frequency of the genes being considered, uses information regarding the specificity of HLA antibodies, and accommodates multiple genetic systems.[31] In simple terms, the cumulative probability is the chance of finding a donor whose HLA and ABO antigens do not react with the recipient's existing antibodies to those two systems, and it is the product of the frequencies of acceptable genes in those two individual systems. We recently compared PRA values and the calculated cumulative probabilities (P_c) of transplantation for sensitized recipients.[31] Some patients with PRA values of 80% to 90%, suggesting difficulty finding a compatible donor, had P_c values of 0.22 to 0.33, a range indicating a much

better chance of finding a donor. Conversely, there were other patients with PRA values below 60% whose P_c values were less than 0.05, indicating more than the expected difficulty in finding a crossmatch-negative, ABO-compatible donor.

The P_c calculation also permits one to estimate how long a patient with antibody would have to wait on the transplant list for an HLA- and ABO-compatible kidney according to the size of the donor pool. For example, with a calculated P_c of 0.01 and a donor pool of 100, the patient would wait an average of one year for a compatible kidney. A patient with a P_c value of 0.001 would wait 10 years in a system generating only 100 donors per year, but would wait only 1 year if the system were expanded to include 1,000 donors. If the P_c value were 0.0001, a donor pool of 10,000 could provide an acceptable donor, since even a pool of 1,000 donors would take an average of 10 years to provide a donor. These are the individuals who are truly "difficult-to-transplant" and who should be focused on and not confused with others who simply have a high PRA value. If we use PRA values and misidentify sensitized patients, we will fail to provide the organ exchange mechanism they need and will find transplants for them only by sheer luck. The alternative is a truly cooperative national sharing effort. We trust that national sharing itself will not be sheer luck.

The recent National Organ Transplant Act promises to offer the framework not only for equitable distribution but also for intelligent sharing of cadaveric organs. Although we physicians cannot control many of the factors affecting the supply of and demand for cadaveric organs, we can incorporate histocompatibility into a national organ sharing effort. This could raise the success rates of the grafts currently most likely to fail, thereby lessening the burden for retransplantation and the degree of sensitization from failed grafts that makes patients wait longer. Precise analysis of patients' sensitization through the calculation of the cumulative probability of transplantation (P_c) should permit local programs to effectively handle patients with low degrees of sensitization and allow physicians to channel quickly into a national access program those patients who are truly highly sensitized.

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