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The high-risk recipient: the Eighth Annual American Society of Transplant Surgeons' State-of-the-Art Winter Symposium

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Abstract: The evolution of organ transplantation has produced results so successful that many transplant programs commonly see recipients with medical risks, which in the past, would have prohibited transplantation. The Eighth Annual American Society of Transplant Surgeons State-of-the-Art Winter Symposium focused on the high-risk recipient. The assessment of risk has evolved over time, as transplantation has matured. The acceptance of risk associated with a given candidate today is often made in consideration of the relative value of the organ to other candidates, the regulatory environment, and philosophical notions of utility, equity, and fairness. In addition, transplant programs must balance outcomes, transplant volume, and the costs of organ transplantation, which are impacted by high-risk recipients. Discussion focused on various types of high-risk recipients, such as those with coronary artery disease, morbid obesity, and hepatitis C; strategies to reduce risk, such as down-staging of hepatocellular carcinoma and treatment of pulmonary hypertension; the development of alternatives to transplantation; and the degree to which risk can or should be used to define candidate selection. These approaches can modify the impact of recipient risk on transplant outcomes and permit transplantation to be applied successfully to a greater variety of patients.

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Organ transplantation has evolved such that programs now commonly transplant recipients with medical risks, which would have been prohibitive in the recent past. These patients with substantially greater comorbidities demand meticulous perioperative and post-transplant care. Each recipient that comes to the transplant center brings a certain risk profile and must be assessed as regards the potential risks that *the particular* patient brings to the transplant procedure. The Eighth Annual American Society of Transplant Surgeons State-of-the-Art Winter Symposium explored high-risk recipients, emphasizing issues that might have previously contraindicated transplantation.

Defining the problem

Organ transplantation inherently involves risk. The patient and family bring risk, but with little choice when the faced with end-stage organ failure. The hospital may develop service to high-risk patients to fulfill an institutional mission or improve its reputation. The community may take pride in the accomplishments of its transplant center. The medical team within the institution also takes risk. Physicians and other medical professionals may view high-risk patients differently, even within the same transplant center. The transplant surgeon is trained to accept and manage risk in the course of surgical education,

transplant training, and devotion to sick patients through the provision of a life-saving alternative, organ transplantation.

Yet, transplant surgeons may come to view high-risk recipients in divergent ways. Practicing in institutions with strict protocols may lead surgical groups to select recipients with low to moderate risk. Others may see accepting high-risk patients a moral and/or worthy challenge, or they may be unwittingly compelled to treat high-risk patients by a disproportionately precarious patient pool.

There are numerous comorbidities and patient demographics that add to risk. Older recipient age unavoidably adds to patient risk. As the transplant community accepts older patients for listing, advanced atherosclerotic vascular and heart disease become more prevalent. Within the last decade, acceptance of patients who are morbidly obese, who have hepatitis C, or those with malignancies has broadened considerably.

The first systematic efforts at organ transplantation began with kidney replacement in the 1960s. At that time, dialysis support and other medical care were rather primitive, and kidneys were transplanted into very sick, although young patients. Between 1970 and 1980, the average patient was still risky compared to today. By the 1980s, transplantation had evolved into a mature and accepted medical-surgical option. With the advent of cyclosporine and other immunosuppressive regimens, success became the expected outcome, and higher risk patients were referred earlier for transplant. In the 1990s, efficacy was well established and demand began to far exceed organ supply. Transplant team members started to see very high-risk patients routinely. The recipient at the extremes of age or with multiple comorbidites, those needing multiple organs, and those requiring extraordinary care came to define modern transplantation.

As the millennium changed, there has been little difference in immunosuppression or surgical technique. However, external constraints upon transplant programs cast risk in a different light. The current regulatory structure includes sanctioning bodies that define standards to which all transplant professionals must adhere. Regulations, however, may potentially stifle innovation or even supersede good clinical judgment. Even well-intentioned regulation of medical care may add risk through unintended consequences. For example, the OPTN policy preferentially allocating kidneys to pediatric recipients was followed by a decrease in pediatric living donor transplants and the subsequent decrease in availability of very good kidneys to other suitable candidates.

Attention to institutional outcomes is a focus of the current regulatory framework, and transplant programs must consider that their outcomes are an important determinant of program certification and reimbursement. This may be a particular challenge when decision-making guided by concern with outcomes may run counter to the interests of the individual candidate. While the concept of stewardship of a precious resource may apply to the high-risk recipient, under many circumstances, transplant represents the option with the greatest potential benefit, indeed the lowest risk option for that candidate, even if that benefit may be less than for other candidates.

The challenge of balancing outcomes, transplant numbers, and costs of organ transplantation is another matter that every program must address. Routinely transplanting high-risk recipients may increase transplant volume, but expanding access to the sickest patients may be the worst of all circumstances: diminished outcomes at high cost. Thus, a transplant center team must make choices that balance saving lives with obtaining results that are acceptable to external regulators. The temptation may be to seek lower-risk recipients. This contrasts starkly with the history of transplant surgery. Beyond external oversight, with the current organ shortage, when is the high-risk candidate too high risk?

Types of high-risk recipients

It is useful to contrast our concept of high-risk with historical precedents. To that end, Dr. John Roberts from the University of California at San Francisco (UCSF) described the long tradition of surgical innovation in transplantation and reminded attendees that the first kidney transplants in 1954 and the first liver transplant in 1963 were extremely high-risk situations (1). In the past, the benefit of transplant was high and the competing use of the organ was low. Today, the competing use of the organ is high, which leads us to consider the limits of recipient risk relative to the value of the organ to others. An example of this is transplantation for hepatobiliary malignancies (2). While five-yr survival had been unacceptably low, the thoughtful development of recipient selection processes has improved survival to match the competing value of that organ to other candidates (3).

Coronary artery disease (CAD) is a risk factor that may affect recipients of all organs, as discussed by George Tellides (Yale). CAD is the single best predictor of mortality in the end-stage renal disease (ESRD) population, accounting for more than

50% of deaths. In kidney recipients, death with graft function is the primary cause of graft loss, and CAD the major cause of death (4). The prevalence of CAD in the ESRD population is approximately 40%, and after kidney transplantation the incidence of new CAD is nearly 25% by 15 yr. Modifiable risk factors such as hypertension and hyperlipidemia are worsened by immunosuppression. Pre-transplant management of CAD is centered on control of modifiable risk factors, screening, and intervention where appropriate. The indications for revascularization are similar pre-, post-transplant and in the general population. Inflammation may link organ dysfunction, allograft rejection and CAD, as markers of inflammation, particularly IL-12 and γIFN, predict cardiac death both before and after kidney transplantation, and rejection episodes predict cardiac death post-transplant (5).

Another example of high risk is the non-liver transplant recipient with hepatitis C (HCV). As explained by Timothy Pruett (University of Virginia), the risk in these recipients is primarily the potential effect of immunosuppression on HCV infection. Post-transplant mortality is increased in HCV kidney recipients, having greater mortality from liver disease and sepsis, but less from cardiac disease (6, 7). However, they still receive a benefit from kidney transplantation (6). The use of HCV positive kidneys not only expands the donor pool but expedites transplantation for HCV+ kidney recipients. Patient survival is similar for HCV+ recipients of either an HCV+ or HCV− kidney, although graft survival is worse with an HCV+ donor. Outcomes are worse when a HCV+ organ is transplanted into a naïve recipient. While 5–7% of the kidney waiting list is HCV+, only 2.5% of candidates are willing to accept HCV+ kidneys. Whether donor transmission of genotypes with worse prognosis into a recipient with a more favorable genotype confers a worse outcome is not presently known.

The risk associated with the HCV+ donor is different in extra renal transplantation. HCV+ heart recipients have lower patient survival than HCV− recipients, and for each recipient group survival is worse with an HCV+ donor. Significant limitations on existing data include a lack of accurate serologic, virologic, and other clinical information. Patients with HCV are not the same, so generalized recommendations are difficult. Making recommendations for HCV+ candidates with compensated cirrhosis, who are not candidates for liver–kidney transplant, is difficult because of a paucity of data. These patients have typically been denied kidney-alone transplant because of concerns about perioperative or post-immunosuppressive liver failure, although this approach is being revisited at selected centers.

The changing definition of recipient risk applies to psychosocial factors as well. Cheryl Jacobs (University of Minnesota) noted that as many as 50% of transplant recipients are non-adherent to their immunosuppressive regimen, and up to 36% of graft losses are related to compliance issues (8–10). Predictors of non-adherence include recipient demographics, prior non-compliance, tolerability and complexity of treatment regimen, mental health, social support, substance abuse, and financial issues. These factors reinforce the importance of mental health and social support assessments at the time of transplant evaluation. After transplant, treatment plans should be as simple and tolerable as possible, with ongoing monitoring for barriers to compliance.

Transplant benefit

Dr. Robert Wolfe (Scientific Registry of Transplant Recipients) discussed the concepts of transplant benefit and life years following transplant (LYFT), a possible component of a modified kidney transplant allocation system (11). Giving priority to candidates projected to have greater LYFT would lead to longer lifetimes overall among kidney recipients. Components of a potential kidney allocation score could be a combination of accumulated dialysis time, a kidney Donor Profile Index (DPI), LYFT, and sensitization. Patients would then be allocated organs having a similar survival potential as might be expected for the recipient. Such a system would maximize LYFT, reduce death with graft function, and permit all candidates the opportunity to receive a transplant.

These discussions set the stage for the keynote debate entitled, ''Road to Nowhere: Are There Candidates That Should Not Be Transplanted?'' ASTS President Goran Klintmalm (Baylor) pointed out that there are many more patients needing transplants than there are suitable organs; thus, deciding on patients that should not be transplanted is an unavoidable necessity. Patients with poor expected long-term survival because of underlying disease or comorbidities, or even those in whom survival is expected but at severely limited capacity should not be considered for transplant. Mark Stegall (Mayo Clinic) suggested that many centers are not transplanting patients who would benefit. Programmatic considerations are increasingly complicating these decisions; centers may turn down high risk, but suitable, patients to

protect their outcomes, and high-risk candidates are too costly and difficult to care for. Many candidates are not referred because of inadequate access to health care, lack of insurance, and variability in both program selection criteria and geographic access. To address this, he proposed (i) more detailed methods of predicting candidate outcomes and assessing programmatic outcomes; (ii) accurately assessing the benefit of transplant; and (iii) ranking deceased donor candidates by comparative benefit. For the latter, it was emphasized that any proposed kidney allocation score will not result in those with lower benefit being shut out from the opportunity for transplant. The underlying question is: Is there a compelling reason to favor utility over equity? which is ultimately a societal question.

Risk reduction

Depending on the organ system, there may be opportunities to mitigate risk by specific interventions. The UCSF down-staging protocols for hepatocellular cancer (HCC) were presented by Francis Yao. The Milan criteria give priority to patients with a single lesion ≤ 5 cm or two to three lesions, none >3 cm in the absence of macroscopic vascular invasion or extra hepatic spread (12). UCSF has championed an effort to downstage tumors outside Milan criteria so that patients become candidates for transplantation (13–15). Response to locoregional therapy is a prognostic marker for improved post-transplant outcome (3). Data presented on 61 patients showed that successful down-staging can be achieved in the majority of carefully selected patients with excellent post-transplant outcomes. Down-staging may select a subgroup of biologically favorable tumors.

J. Wesley Alexander (Cincinnati) presented a series of morbidly obese patients with chronic renal failure (CRF) who underwent gastric bypass surgery (GBP) either before or after transplant. Dr. Alexander noted that obesity negatively impacts both access and outcomes in kidney transplantation (16). The Cincinnati experience included 10 patients who became morbidly obese post-transplant and then had GBP, and another 48 patients who had GBP and then either were transplanted ($n = 14$), became candidates, or had improvement in native renal function ($n = 9$). The majority were open cases with minimal morbidity and mortality: no leaks, splenic injuries, transfusions, deep wound infections, or perioperative deaths. All patients had a sustained decrease in BMI and in comorbid conditions (diabetes, hypertension, and hypercholesterolemia) at 12 months. The indications for GBP in renal failure or renal transplant patients, he suggested, should be the same as for the general population.

Abbas Aredhali (UCLA) discussed the management of heart transplant candidates with pulmonary hypertension (17). Patients with fixed pulmonary hypertension (pulmonary vascular resistance [PVR] > 4, transpulmonary gradient [TPG] > 15) are not considered heart transplant candidates. While in the past these patients have been heart–lung transplant candidates, recently they have undergone chronic pulmonary vasodilator therapy or received left ventricular assist devices (LVADs) as a bridge to heart transplant. About half of candidates with ''fixed'' disease receiving sildenafil therapy were successfully transplanted, and a randomized trial is in progress (18). A report of 10 patients with heart failure and pulmonary hypertension were treated with LVADs with significant reduction in PVR and TPG; five of these were successfully transplanted (19).

Peter Gruber (Children's Hospital of Philadelphia) discussed another aspect of the management of high-risk transplant candidates: maximization of non-transplant options. He demonstrated that in patients with hypoplastic left heart syndrome (HLHS), survival following palliative surgery for HLHS is nearly equivalent to that following transplantation (20, 21). Although transplant recipients are generally those in whom palliative options are not feasible or have failed, the ability to manage HLHS without transplant allows immediate treatment and minimizes waiting times and waitlist mortality for those who do require transplant.

Sunday debates

The first debate focused on the choice of live donor grafts versus deceased donor grafts in pediatric kidney transplantation. Albin Gritsch (UCLA) argued for the continued preferential use of live donor grafts in children because of their superior short- and long-term outcomes, immediate function, and elective timing of procedure. The superiority of live donor grafts is particularly true in the youngest recipients under two yr of age. Fairness to those awaiting a deceased donor organ was also cited. Ken Andreoni (University of North Carolina) countered that most pediatric transplants occur in larger children, age 13 or older; fewer than 20% of pediatric transplants are carried out in children less than five yr of age. The question was posed: If a child had only one potential live donor, would you use that live

donor now, or take an excellent deceased donor graft offer that comes rapidly in the current pediatric allocation system? Dr. Andreoni argued that nearly all children are expected to outlive their first renal transplant, and outcomes for excellent deceased donor grafts at five yr compare favorably to living donor organs. The only realistic chance of obtaining a future pre-emptive second transplant for today's pediatric recipient, who is tomorrow's adult recipient, is to have a waiting live donor.

Mark Ghobrial (UCLA) and Alan Langnas (University of Nebraska) then debated liver retransplantation for recurrent hepatitis C. Dr. Ghobrial, arguing the pro side, pointed out that in the Baylor experience, outcomes for a first retransplant for primary non-function and all other causes were equivalent at 10 yr (22). He stressed that poor outcomes in HCV retransplant recipients are strongly tied to the use of donors over age 60 (23). The tendency for patients with recurrent HCV to be older and have renal dysfunction also leads to increased early death after retransplantation (24). Four-yr graft survival was similar for retransplantation in HCV and non-HCV recipients in both the UNOS database and the UCLA experience (25). However, these HCV retransplant recipients have a 31% higher covariate-adjusted mortality risk compared to non-HCV recipients (26).

Dr. Langnas argued that the real question is whether we should retransplant anyone, including hepatitis C recipients, because 1000 people a year die on the wait list prior to their first opportunity at liver transplantation. In addition, post-transplant medical treatment is effective in less than one-third of HCV recipients, with 20–40% of recipients displaying cirrhosis by five yr. Because we currently limit transplantation to those patients that will have an acceptable outcome, and because one-yr survival is 50–60% after retransplant, should a first transplant give someone special access to a second transplant (27, 28)? He also noted that more patients are being refused retransplantation today, especially with MELD scores > 30, because of poor outcomes, and that the answer to HCV recurrence is better medical therapy, not retransplantation.

In the final debate, economists Drs. Mark Schnitzler and Roger Evans discussed whether outcomes for transplants should be risk adjusted. Dr. Schnitzler (St. Louis University) argued that the OPTN data have significant predictive power for transplant outcomes, but some variation is because of other comorbid pre-transplant conditions that are not measured, as well as center performance and random variation. By using more stringent measures of comorbidities, such as the Elixhauser, Charlson, and CCS scales, some of the previously unmeasured variance in outcome can be explained (29).

Dr. Evans disclosed some major financial problems of Medicare and Social Security and stressed the need for fiscal responsibility in all health care. He noted that transplantation is becoming more expensive in the short term and less cost effective in the long term as we transplant older and sicker individuals. Transplant patients account for a disproportionally high share of annual health care expenditures. The question was raised: For what should we adjust risk? Risk adjustment could include the concepts of case-mix, disease severity, comorbidity, clinical factors, socioeconomic status, age, ethnicity, and disability status. Candidate and donor selection criteria have been relaxed (risk increased) in the name of saving more lives without consideration of the increased cost involved. Conservative patient and donor selection assure the cost-effectiveness of transplantation by improving outcomes and containing costs, thus responsibly promoting *population* health. In summary, Dr. Evans argued for consensus guidelines for patient and donor selection to minimize variation. Given scarce resources, current financial realities, and competing demands, transplantation could become viewed as an unworthy public health investment.

Summary

While risk in the organ transplant recipient has always been inherent in transplant surgery, the assessment of risk has evolved with changing eras and environment. The acceptance of risk associated with a given candidate today is often made in consideration of the relative value of the organ to other candidates, the regulatory environment, and philosophical notions of utility, equity, and fairness. Modifications of the impact of recipient risk factors on transplant outcomes, through more precise identification and characterization of risk, interventions that reduce risk, and the development of alternative therapies to transplantation, can play important roles in the overall management of risk among transplant candidates and recipients.

Conflict of interest

None of the authors, or their family members, has a financial interest in a business or commercial entity, or an intellectual property interest, that relates to this manuscript.

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