Invited Comment

In the queue for a cadaver donor kidney transplant: new rules and concepts in the Eurotransplant International Foundation

Johan De Meester, Guido G. Persijn, Frans H. J. Claas and Ulrich Frei

Eurotransplant International Foundation, Leiden, The Netherlands

Queuing is accepted as long as one knows, understands and follows the rules. The waiting for a kidney transplant does not get around this basic concept. A lot of energy has been put into the development of rules, mainly dedicated to the process of kidney allocation, aiming at an optimal proportion between justice and efficiency [1]—the medical ethical criteria. Additionally, the allocation programme had to be supported by the vast majority of the renal transplant programmes involved, and to be perceived as fair and equitable by all potential transplant candidates and society. Whereas in earlier times the allocation algorithms and their adjustments were made by common sense, intuition and scientific progress, nowadays one advocates the use of computer simulation studies, which are more capable of predicting the outcome of a particular system and/or proposed change [2,3].

The new allocation system of Eurotransplant

In March 1996, the international organ exchange organisation, Eurotransplant [ET], switched to a new kidney allocation system that was based on the kidney allocation computer model study of Wujciak and Opelz [4]. The basic model—a point system with a limited number of allocation factors—was tailored to the actual ET situation without changing the original goals; prevention of long waiting times, achievement of good HLA-matching and corresponding graft outcome, optimal balance between national donor kidney procurement and transplantation, and improved transplant logistics aiming at short cold ischaemic times. All kidney offers would be made for a particular patient. In a rather abrupt way the new allocation system attacked the distorted situation [5] that had prevailed at the time of implementation, but now one gradually moves to a new steady state, closely following the course predicted by the computer simulation studies. It is clear that a better trade-off between waiting time, HLA-matching, and kidney donation/transplantation will be realized, in comparison with the previous system which was aimed primarily at maximum HLA-matching.

Remaining problems

Computer-modelled allocation programmes by themselves, however, will not solve the waiting problem. Attention should be paid to (i) equal access and to standardized listing practices, i.e. an equal starting point for all candidates, and (ii) the definition and justification of the criterion of ‘urgency’ in renal transplantation. The impact of the changing donor kidney quality, as kidney donation criteria are more and more liberalized, is difficult to anticipate. In this respect, controlled pilot projects might be the only appropriate solution. Finally, the transplant physician should be aware of the chances of selection for any transplant candidate. What will the theoretical number of kidney offers be if case restrictions are made on donor age, HLA-match requirement, etc.? With regard to these items, new rules and concepts have been worked out in the ET organ exchange organisation.

Eligibility criteria and minimal listing criteria for renal transplantation: new concept — new rule for waiting time?

It is commonly assumed that patient acceptance policies for transplantation and time point in the evolution of renal failure when patients are listed are similar for all patients in all centres. This is based on the consideration that all nephrologists act according to the latest medical and scientific data. This is not true: everyone will remember a patient who had been declined as a transplant candidate in one centre and who was later accepted for transplantation in another transplant programme.

The indication for a kidney transplant is irreversible end-stage renal failure, necessitating renal replacement therapy for patient survival. While a consensus is largely present on absolute contraindications, decision criteria differ in the presence of factors which may
adversely influence the graft and/or patient outcome after transplantation. Such factors comprise re-transplantation, obesity, non-compliance, recurrence of primary end-stage renal disease, concurrent or past co-morbidity [6]. In 1992, Briggs [7] noted considerable disparity in the selection criteria for transplantation in the United Kingdom. In 1998 a new survey on the current criteria for the evaluation of adult candidates for a cadaveric renal transplant has been carried out in Europe. It was coordinated by the renal transplant programme of Berlin Charité—Campus Mitte (personal communication, H. H. Neumayer, L. Fritsche). The results are eagerly awaited.

From an allocation-technical point of view, the point of time in the evolution of renal failure when the patient is listed as a transplant candidate is more crucial, since waiting time is an allocation factor in each kidney allocation system. It is often the sole criterion to prioritize patients who are equally eligible for a donor kidney. In its most simple calculation, waiting time is defined as the number of days the patients have accrued between the time of listing and the day of the kidney match run. Often, additional conditions after this straightforward calculation of waiting time. They may be time periods which are not counted as waiting time, e.g. as long as relevant match data are absent (ET) or when the patient is (temporarily) not eligible for a transplant. The latter occurs in the renal allocation procedure of the United Network for Organ Sharing (UNOS-USA): as of the 30th day of non-transplantability, the patient no longer accrues waiting time.

Similar to late referral to dialysis units [8], dialysis doctors might delay referring their patients to a transplant programme. Causes of such late referral include medical pathology such as significant intervening non-renal pathology such as a cardiovascular event or the occurrence of a tumour and its treatment, as well as non-medical conditions, such as financial policies, lack of interest of the patient for social reasons or fear of surgery or transplant complications. Listing prior to the start of dialysis (pre-emptive listing) has become more and more popular. This is true in particular for transplanted patients with a failing graft, and also for paediatric patients. Better graft survival, and decreases in both growth failure and delay of neuropsychological development have been reported in children receiving a pre-emptive renal transplant [9]. Occasionally transplant programmes list patients earlier than a transplant is actually required, in an effort to accelerate waiting time.

In 1994, waiting time for cadaveric donor transplantation was analysed (personal analysis) using the ET renal allocation system, as the time the patient entered the ET renal transplant waiting list in 1993. There were striking differences between the ET countries: in Belgium and Austria 50% of the cohort was transplanted at 21 months, while the same transplant rate was obtained in The Netherlands at 36 months and in Germany at 40 months. It is likely that the differences in donor kidney availability, relative to the active kidney transplant waiting list, are responsible for the differences between countries. Austria and Belgium have a kidney donation rate meeting about 40% of the active waiting list, in contrast to only 33% for The Netherlands and 20% for Germany. There may be other causes as well. Another ET study [10] analysed patients in The Netherlands with long waiting times (>5 years). It was concluded that the vast majority of the patients were placed on the waiting list at the time the dialysis centre started its work-up of the patient as a potential transplant candidate. The patients were listed as ‘non-transplantable’ until the patient has been fully assessed for, and accepted by, the transplant programme. The time the patient had already spent on the waiting list, i.e. often 6–9 months, was counted as official waiting time. In other ET countries, it is common practice to enter the patients on the waiting list only after they have been definitively accepted by the transplant programmes.

The wide variability in patient listing practices, which significantly affect allocation schemes makes it urgent to standardize criteria for defining the waiting time, to the so-called minimal listing criteria [11]. A consensus conference on standardized listing criteria for renal transplant candidates in the United States [12] reviewed scientific data concerning to the definition of end-stage renal disease and the different handling of particular patient groups, e.g. diabetics or children. A glomerular filtration rate of less than 18 ml/min (as calculated by a formula, using serum creatinine, age, gender, race, serum urea nitrogen and serum albumin) would render a patient eligible for listing, and for accrual of waiting time, if the patient has a progressive renal disease. Diabetes or other specific renal diseases should not be handled differently, but care should be taken that children are not disadvantaged in any way. Similar discussions have started in Germany and The Netherlands, following the recent implementation of their respective donation and transplant laws. A German proposal would allow pre-emptive entry on the waiting list, starting at the moment when preparations for dialytic therapy are made (e.g. creation of an AV-fistula). The pre-emptively listed patients could participate in the renal allocation procedure, although they cannot obtain points for the allocation factor ‘waiting time’, since the accrual of waiting time is only possible at of the moment the patient has started with chronic dialytic treatment. Such a strategy might put patients who have opted for peritoneal dialysis and who receive their dialysis access rather late at a disadvantage.

As of January 2000, waiting time will be defined in the ET renal allocation system, as the time the patient has been dialysed, without interruption, regardless of the therapeutic option i.e. haemodialysis or peritoneal dialysis. While this may seem fair for patients who were referred late for transplantation or who have to wait to exclude recurrence of a tumour, this re-definition of waiting time might, contrary to its intention, promote late referral to a transplant programme, since patients are already accruing waiting
time although they are not yet officially on the waiting list.

In organ exchange organisations, another set of rules deal with waiting time. If a patient has had an early kidney graft failure the waiting time, accrued prior to this failed transplantation, would still be counted when the patient is re-listed for a repeat transplantation. The UNOS Kidney/Pancreas Transplantation Committee only allows for waiting time reinstatement under the following conditions: (i) hyperacute rejection in the presence of a current negative cross-match, and (ii) graft failure due to non-immunological causes within the first 2 weeks. In contrast, the ET Kidney Advisory Committee has defined early kidney graft failure as any graft failure within the first 3 months post-transplant. Recently, the condition that such a patient has to be re-listed within 1 year after the failed renal transplant was dropped. It was felt to be clinically unsound to enforce such return on the waiting list.

Simultaneously, there was concern that—in view of the current tendency to use, more often, kidneys from so-called marginal donors—any rule of waiting time reinstatement might encourage some transplant programmes to proceed with a transplantation against all odds. An audit of the cases of waiting time reinstatement will therefore be indispensable.

It is clear that as an allocation factor, waiting time is far from simple. It is even questionable as medical criterion. Therefore, proper and uniform guidelines for listing (and de-listing) should be defined.

**High urgency kidney transplantation: old concept—new rule?**

The option ‘highly urgent (HU)’ kidney transplantation ‘goes back to the early days of dialysis and transplantation [13]. It implies rescue renal transplantation in order to keep the patient alive. In exchange for a high priority HU kidney transplant, any preference for a minimum degree of HLA-matching must be skipped. In the presence of a negative cross-match any kidney suitable for transplantation, regardless of the HLA-matching, had to be accepted and transplanted. Imminent lack of haemodialysis access, often in combination with exhausted possibilities of or even contra-indications against peritoneal dialysis, accounted for 60% of the HU requests. Severe polynephropathy and/or inability to cope with the dialysis treatment—often accompanied by suicidal thoughts—accounted for another 20%. The remaining 20% was the result of a variety of conditions, such as severe renal osteodystrophy with metastatic calcifications, recurrent episodes of fluid overload, or poor general condition.

Despite the marked advances of dialytic therapy, many transplant programmes in the ET area, even today, apply for the HU transplant option. The absolute number per year in the 1970s, 1980s and 1990s has remained similar, i.e. 60–70. Of course, today this represents a smaller fraction of the total transplant volume: 2 vs 4–5% in the past. The relative frequency of the major indications has not changed, but new indications have been accepted: immuno-adsorption protocols, creation of a neo-bladder, and haemorrhagic cystitis following kidney graft failure after a kidney–pancreas transplantation, caused by a functional bladder-drained pancreas graft. It is important to note that the mortality on the HU renal transplant waiting list is now virtually nil, in contrast to the early 1970s. The term ‘High urgency’ in renal transplantation no longer stands for ‘life-saving’, in contrast to what is still true in cardiac and liver transplantation.

The need for a HU category has regularly been questioned in the ET Kidney Advisory Committee. The majority of the centres do not make a HU request, (i) because they want to adhere to their minimal HLA-transplant. Recently, the condition that such a patient appears at the top of the allocation list. Waiting time is far from simple. It is even questionable as medical criterion. Therefore, proper and uniform guidelines for listing (and de-listing) should be defined.

**ET senior programme: old-for-old concept**

Transplantation is advocated as the best option of renal replacement therapy. Following the gradual increase of elderly patients on dialysis [14], the same trend is noted in the field of transplantation [15]. In ET the number of patients aged 65 years or more who are registered for a first cadaveric renal transplant increased from 196 (4.7%) in 1993 to 301 (7.0%) in
1998, a 50% increase compared to the overall 5% increase.

Mortality inevitably increases with age. Therefore the chance of receiving a transplant while on the waiting list is potentially low for the elderly patient. Using a competing risk analysis technique, we compared the elderly patients (65+ years) and those aged 16–55 years, who were registered between 1992 and 1995. The major difference in outcome on the waiting list at 3 years was not the chance of transplantation (44% vs 47%) in the elderly and young groups respectively but the risk of being removed because of poor condition or death. This risk was three times higher in the elderly than in the young (32 vs 9%).

In addition, many registry reports indicate a lower patient survival after transplantation for the elderly patient, although the kidney graft survival itself would not be jeopardized (death with functioning graft) [16,17]. In a time-dependent non-proportional Cox model [18] of elderly patients (65+ years) listed for transplantation between 1993 and 1996 in the ET area, renal transplantation did not confer a survival benefit after 3 years of follow-up (personal communication, Jacqueline Smits).

In response to the persistent shortage of donor kidneys, older donors are nowadays more carefully evaluated for potential kidney donation. One is aware of an increased risk of initial non-function, and of lower short-term and long-term graft survival. Decreased nephron mass, with a lesser functional reserve after an insult to the graft, e.g. rejection, delayed graft function or hyperfiltration, is presumably the main cause.

Taking into consideration the intrinsically lower graft survival of an elderly donor kidney and the decreased life-expectancy of an elderly recipient, several experts proposed the idea to establish a senior donor, recipient pool: the ‘old-for-old’ programme. A retrospective UCLA study [19] provided evidence that such a protocol was sensible. Seniors (61+ years) receiving kidneys of older donors (61+ years) tended to have less graft failure compared to the younger recipients, while senior recipients of a younger donor kidney experienced a higher rejection rate compared to younger recipients. An effect of HLA-matching was not present in the group of senior recipients/senior donors. In an ET multivariate study investigating 1-year graft survival of the old-for-old couples while censoring for death with functioning graft, optimal results were found in case of a first transplant of a non-sensitized elderly patient.

As of January 1, 1999, a prospective old-for-old allocation programme has been implemented in the ET organisation, the so-called ET Senior Programme. In practice, the transplant programme reporting an elderly donor (age 65+ years) has the possibility to select from the allocation list any local elderly patient who fulfills the following criteria: age 65 years or more, not sensitized and awaiting a first transplant. Since short cold ischaemia times are thought to play a more important role than HLA-matching, an efficient organisation of the procurement and transplant procedure, supplemented with high quality cross-matching, is needed for the success of this endeavour. Also, close management of the elderly transplant candidates is a condition sine qua non, in view of their more frequent morbidity while on dialysis.

**Immunological matching: matchability concept**

The positive influence of HLA-matching on kidney graft survival has been demonstrated for more than 25 years [20–22]. Realizing that a donor kidney with zero HLA-mismatches is only for the happy few, thresholds of maximum mismatch and/or minimal sharing of HLA-antigens have been identified, as a proxy for an ‘optimal HLA-matching’. In this respect, it should be noted that between 1988 and 1996 the ET renal transplant programmes were bound to the sharing of at least one HLA-B and one HLA-DR antigen. Even today many transplant programmes continue to use these minimal requirements of HLA-matching, as is apparent from the centre-specific default HLA-matching profiles, stored in the ET kidney allocation programme.

What are the chances of receiving such a ‘good HLA-matched’ donor kidney (within a ‘reasonable’ waiting time)? For that purpose, several ‘matchability’ or ‘match diagnostic’ indexes [23–27] have been developed, expressing the relative likelihood of receiving a donor kidney with a ‘good HLA-match’. These ‘matchability’ indexes help the transplant physician to set the appropriate minimal HLA-match requirements, in relation to the patients HLA phenotype, and to estimate the chances of a donor kidney, fulfilling these requirements. It goes without saying that if a HLA-match requirement is set too high then the patient will be eligible for few donor kidneys and will have to wait long for transplantation. And, in contrast, if it is set too low, the patient might experience a greater risk of graft failure or even death.

Information provided by the indexes should be interpreted in the proper context. First, a kidney allocation programme is often not 100% HLA-matching driven; other allocation factors are also involved.

Secondly, for the patient several donor HLA-antigens may be unacceptable, reducing substantially the number of ‘good HLA-matched’ donors. Regrettably, there is no general consensus about the definition of unacceptable donor HLA-antigens. In any case, HLA-specific antibodies, detected in the actual patient’s serum, undoubtedly identify unacceptable donor HLA Class I antigens and predict a positive crossmatch which is the final pre-transplant test. The relevance of antibodies to the following is controversial: (i) HLA Class II HLA-antigens, (ii) HLA Class I antigens which were identified only in historical sera, (iii) the donor HLA-antigens which were mismatched in previous transplantations and, if applicable, (iv) the HLA-antigens of the (sexual) partner. All these additional immunological restrictions affect almost 30% of the
active ET kidney-only waiting list (n = 11789; January 1, 1999). Ideally, a ‘matchability’ index should also consider the unacceptable donor HLA-antigens.

Immunological matching is only relevant when there is a sufficiently large donor catchment area [2]. The more donors, the higher the chance of a ‘good’ match. Any policy to maximize the number of zero HLA-A, B, DR mismatch transplants should operate on the largest possible donor pool. The same reasoning should be applied for patients with a very restricted suitable donor pool, such as highly sensitized patients. If a kidney allocation programme pays too much attention to the possibility of local or regional transplantation, one may not expect to obtain excellent HLA-matches, due to the imbalance between small donor pool and short waiting list.

When the ‘matchability’ index is applied in a kidney allocation scheme, it will prevent patients more easily matched from being transplanted with poor HLA-matches, while simultaneously the accumulation of poorly-matchable patients on the waiting list is avoided. This effect has been shown in the new ET kidney allocation system. All new registrations were divided into four equal groups of matchability: high, high average, low average and low. During the previous ET kidney allocation system, any snapshot analysis of the waiting list showed a significantly lower percentage of high matchability patients (18%) and a higher percentage of low matchability patients (32%). Nearly 3 years after the introduction of the new allocation system, the current waiting list consists of 21% high matchability patients and 27% low matchability patients. This switch was also noted in the transplant population: comparing the former and new scheme, the proportion of high matchability patients decreased from 29 to 24% while that of the low matchability patients increased from 23 to 25.5% (with a transient peak of 31% in the first year of the new system). This re-arrangement of the transplant population did not lead to a much poorer HLA-A, -B, -DR match distribution. The percentage of zero HLA-A, B, DR mismatched transplants remained unchanged (22%), and there was only a marginal increase of the proportion of patients receiving a kidney with four or more HLA-A, B, DR mismatches (from 7 to 12%). The above-mentioned effects on waiting list and on transplant population, however, are less pronounced in the ET countries with a strong HLA-matching tradition (Belgium, The Netherlands).

Conclusion

The donor supply stagnates, but changes qualitatively. Furthermore, there has been constant progress of treatment of end-stage renal disease. The increasing demand for a kidney transplant calls for reflection, consideration and implementation of new rules and concepts. Strict listing criteria, sound immunological and non-immunological donor requirements and sufficient (graft and patient) survival benefit are essen-
tial aspects of kidney allocation systems. Continuous flexibility and solidarity of transplant programmes are of the utmost importance if each transplant candidate is to derive maximum benefit.

References

8. Limeire N. The referral pattern of patients with ESRD is a determinant in the choice of dialysis. Peritoneal Dial Int 1997; [Suppl 2]: 161–166
26. Wujciak T, Opelz G. Matchability as an important factor for kidney allocation according to the HLA Match. Transplant Proc 1997; 27: 1403–1405