ORGAN ALLOCATION SYSTEMS AND MANAGEMENT OF THE RENAL TRANSPLANT WAITING LIST

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A b s t r a c t: In 1996 the EUROTRANSPLANT organisation, which currently includes the member-states Austria, Belgium, Germany, Luxemburg, the Netherlands and Slovenia, changed its policy of renal donor organ allocation to the new algorithm ETKAS (Eurotransplant Kidney Allocation System). Its main goal was to shorten the average and maximum waiting time, adjust for rare HLA phenotypes and homozygosities, achieve a reasonably balanced exchange rate among countries with variable organ procurement rates and guarantee an acceptable HLA match distribution and a optimal overall transplant success rate. Several additions have been introduced since then such as the Eurotransplant Senior Programme, which allocates kidneys from donors older than 65 years to recipients over the age of 65. Due to constant refinement the system has achieved its major goals.

Key words: kidney transplantation, organ allocation, waiting list.

Introduction

As HLA matching is still an important factor the individual waiting time before transplantation for a patient with end-stage renal disease is still highly variable. Therefore special attention has to be paid to the optimum medical management of the patients on the transplant waiting list, especially as far as cardiovascular disease surveillance is concerned.

The annual incidence of end-stage renal disease is rising continuously by about 5% [1, 2]. In 1994 4,345 patients underwent renal replacement therapy in Austria, and only 10 years later the prevalence increased to 6,564 [3]. As the prognosis of patients on dialysis is still poor, transplantation is attempted whenever possible, reducing long term mortality by 48–82% [4]. Within the Eurotransplant organisation approximately 12,000 patients are currently registered on the renal waiting list, but only about 3,000 grafts can be allocated each year due to donor shortage [5]. In an effort to increase organ supply, kidneys from so-called "marginal" donors have been transplanted more frequently, although the outcome on average is worse. Even though there is no uniform consensus on which donor factors preclude a successful long-term outcome [6] there is little dispute that donor age is the most important single parameter affecting long-term graft function and, as shown recently, even recipient mortality [7–12]. This is particularly remarkable as the expansion of the donor pool during the last decades has been mostly achieved by extending the upper age limit. In 1987 a donor older than 30 years was the most likely reason for transplant physicians rejecting an offer; in 1996 this threshold had shifted to 60 years [13, 14]. Within Eurotransplant 162 out of 1,456 (11.1%) donors were older than 65 years in 1998, but 249 out of 1,507 (16.5%) in 2003 [15]. In face of these developments it is crucial to allocate organs based on defined rules. The following pages will provide an overview of the allocation scheme used by the EUROTRANSPLANT association. Furthermore, a short summary of other allocation algorithms will be given and finally some aspects of the management of the waiting-list patients will be discussed.

The Eurotransplant Kidney Allocation System (ETKAS) [16]:

Eurotransplant, founded by Jon J. van Rood in 1967, was initially a registry of renal transplant candidates with the primary aim of optimising HLA matching. The organisation has expanded continuously since then and the current mission statement includes such goals as:

• the achievement of an optimal use of available donor organs

• the guarantee of a transparent and objective selection system based on medical criteria

• the assessment of the importance of factors which have the greatest influence on transplant results

• scientific research to improve the results of transplantation

• the support of donor procurement to increase organ supply

• and the promotion, support and coordination of organ transplantation in the broadest sense of the terms.

Still, however, one of the major tasks of Eurotransplant is the allocation of donor organs, probably the most sensitive and fragile issue in medicine next to triage. The allocation rules used currently (Eurotransplant Kidney Allocation System or ETKAS) are based on a consensus among the participating countries of Austria, Belgium, Germany, Luxemburg, the Netherlands and Slovenia, representing a population close to 118 million. ETKAS was implemented in 1996 and has been refined continuously since then in order to shorten the average and maximum waiting time, adjust for rare HLA phenotypes and homozygosity, achieve a reasonable balanced kidney exchange rate among countries and guarantee an acceptable HLA match distribution and optimal overall transplant success rate.

All kidneys (including organs from non-heart-beating donors in all countries with the exception of Germany) procured in the Eurotransplant region are allocated using the algorithms delineated below. However, combined transplantations of a kidney and a non-renal organ have priority over all categories of kidney-only transplantations.

Urgency codes and special programmes:

Transplant candidates can be classified on the waiting list using urgency codes. These codes combine aspects of transplantability (yes or no, i.e. not transplantable or NT), medical urgency (high urgency, HU) and the most recent level of allosensitization (< 6% percentage of panel reactive allo-antibodies, transplantable or T, ≥ 6 but < 85%, immunized or I and $\geq 85\%$, highly immunized or HI). In order for a patient to be accepted by Eurotransplant, HU inclusion criteria have to be met (such as lack of access for either haemodialysis or peritoneal dialysis, severe neuropathy, etc.).

Furthermore, candidates can be registered within special sub-programmes. The Acceptable Mismatch (AM) programme, which is run for every post mortem kidney donor, includes patients with a history of a percentage of panel-reactive antibodies $\geq 85\%$ in two consecutive 3 monthly screenings. The patients do not necessarily need to be highly immunised at the time of organ matching. The programme identifies HLA-A, -B and -Dr mismatches not resulting in a positive cross-match by checking against which HLA-A, -B and –Dr antigens the recipient has not yet reacted with allo-antibodies. Further minimum requirements for organ allocation are the sharing of one HLA-B and -Dr antigen, no unacceptable donor antigens and repeated mismatches and a negative cross-match result in currently sensitised AM patients.

The Eurotransplant Senior programme (ESP) allocates kidneys from $\geq$ 65-year-old post mortem donors to $\geq$ 65-year-old recipients. In order to keep the cold ischaemia time as short as possible no HLA typing is performed and the organs are transplanted on a local (Austria, Belgium/Luxemburg, Slovenia), re-

gional (Germany) or national (Netherlands) level. Only if kidneys cannot be allocated within the ESP are they reported to ETKAS, after HLA typing.

Blood group rules:

AB0 incompatible kidney transplants are not allowed. Within the AM programme AB0 compatibility is mandatory (i.e. A to A and AB, B to B and AB, AB to AB and 0 to A, B and AB). Blood group 0 000 HLA mismatch grafts and organs within the ESP programme can be allocated to B and 0 recipients. For patients with $\geq$ 1 HLA mismatch blood group 0 kidneys are matched to blood group 0 recipients only.

ETKAS point score system:

For kidneys that are not allocated via ESP, potential recipients are sought first within the AM programme. If no suitable candidate can be identified the search continues by looking for patients with a complete HLA match. If several of these are available they are ranked with the help of a point score system as are all others in case no 000 HLA match can be obtained. The patient with the highest point score is ranked on top and receives the first offer. If this offer is rejected, all the following are made in descending order. The number of points awarded is based on several variables, which include the urgency status, HLA match grade, mismatch probability, waiting time, a distance factor and the national balance. Transplant candidates with the urgency code HU receive a bonus of 500 points. Paediatric patients (< 16 years old at the time of Registration) receive a bonus according to their age at the time of registration (< 6 years 100 points, $\geq$ 6–11 years 33.3 points, which is converted to 66.6 points at the 11th birthday, and $\geq$ 11 and < 16 years 66.6 points). Furthermore, in children the points for HLA antigen matching are doubled. In general each HLA-A, -B and – Dr antigen shared is rewarded 66.67 points. The mismatch probability is a calculation of the probability of receiving a kidney offer with 0 and 1 broad HLA-A, -B or -Dr mismatch based on 1000 kidneys offered taking into account the AB0 blood group rules and the PRA screening using data from the Collaborative Transplant Study database for a Caucasian donor population. Upon registration the date of the patient's first dialysis or date of reinstitution of dialysis after a previous kidney transplantation is counted as the first day for the calculation of the waiting time. A patient who is registered with the immediate previous kidney transplantation having failed within 3 months after transplanttation is eligible for the return of waiting time. Per year waiting time, in most countries 33.3 points can be acquired. The points for Germany are different (50) to compensate for the difference in points acquired for the regional bonus (see below). Pre-emptive transplant candidates can be registered, but receive no points for waiting time as they have not yet started dialysis. Local recipients (i.e. candidates from the centre where the donor is from) receive a bonus of 100

points in Belgium / Luxemburg and Slovenia and 200 points in Austria. In Belgium / Luxemburg and Slovenia a regional bonus of 100 points is appointed (one or more transplant centres in the same region as the donor centre), in Germany regionally 200 points are awarded because there is no local bonus. National recipients receive 100 points in Austria, Belgium / Luxemburg, Germany and Slovenia. All Dutch patients receive 300 national points. Once every working day for the period of the immediate previous 365 days, the difference between the number of kidneys procured and exchanged for transplantation in and between each country is calculated. A negative balance for a country is defined as more kidneys being procured than transplanted, a positive the other way around. The national balance points are then calculated as the highest import balance minus the recipient country balance times 10.

Other organ-allocation systems:

Organ allocation in other regions of the world is organised somewhat differently. In countries with a very high organ supply (e.g. Spain with an exceptionally well developed deceased organ procurement system or Scandinavia with a very high living donor rate) mostly local sharing is attempted. Large minorities within the population as in the UK or the USA lead to an inequity of access to organs if the focus of allocation is too much on tissue-matching and therefore in these countries more emphasis is put on non-HLA factors.

Management of the waiting list:

Deceased donor transplantation is unique among surgical procedures as it is an urgent procedure performed in an elective population. Because of the inclusion of histocompatibility matching in the allocation algorithm it is not possible to accurately predict when a given patient will be called for transplanttation. Transplant programmes are therefore faced with the challenge of attempting to ensure that large numbers of patients, most of whom are not even under their direct care, are medically cleared for transplant at all times. It is obvious that the allocation algorithm has an immediate impact on the medical management of the waiting list. If mostly non-HLA factors (like waiting time, for example) are considered, it is more possible to predict the time of transplantation and therefore the pre-transplant medical evaluation can be planned more precisely. Probably this is also due to differences in allocation algorithms which have until now preclude a consensus as to how, when and at which frequencies to evaluate potential transplant recipients [17].

Without any doubt, however, one of the most crucial elements of the medical management of waiting list patients is the cardiac evaluation scheme. It is generally accepted that cardiovascular disease is one of the most frequent causes of death with a functioning graft. Even though the incidence of serious

cardiovascular events is reduced in the long term after transplantation when compared to patients on dialysis (and even when compared to those on the waiting list) the risk sharply increases during the post-operative period [18]. In order to decrease the risk several screening guidelines have been proposed; none of them, however, have ever been tested rigorously in a prospective manner in order to evaluate their clinical benefit or cost-effectiveness. Kasiske and co-workers proposed a risk-stratified screening strategy which has been adopted by most transplant centres, saving especially invasive testing for high cardiovascular risk patients [19]. The situation is even more unclear with regard to the method and frequency of repeated testing in a situation of prolonged waiting time is handled optimally [20]. The situation is even more complicated as until now the predictive value of cardiovascular testing in this special situation has been unclear. As an example, it has been proposed not to accept patients with heart failure and an ejection fraction of less than 30% because of the poor prognosis associated with this constellation after transplantation. Indeed the latter has been confirmed recently; however, it also has been shown that the pre-transplant left ventricular function is an extremely poor indicator of the post-transplant situation [21].

In summary prospective studies are needed to define the optimum programme which is both clinically beneficial and cost effective. Until these are available, local adaption of published guidelines seems reasonable [22–26].

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Р е з и м е

СИСТЕМ ЗА ДОДЕЛУВАЊЕ ОРГАНИ И ВОДЕЊЕ НА ЛИСТА НА ЧЕКАЊЕ ЗА РЕНАЛНА ТРАНСПЛАНТАЦИЈА

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Во 1996 година организацијата ЕВРОТРАНСПЛАНТ, која во моментов ги вклучува земјите-членки Австрија, Белгија, Германија, Холандија и Словенија ја смени практиката за доделување на донираните бубрежни органи спored новиот алгоритам ЕТРАС (Евротрансплант ренален алокациски систем). Главната цел беше да се скрати просечното и максималното време на чекање, да се адаптира спored ретките ХЛА фенотипови и хомозиготи, da постигне разумно избалансирана стапка на измена помеѓу земјите со различна побарувачка на органи и да се гарантира една прифатлива ХЛА складна дистрибуција и севкупна оптимална стапка на трансплантациски успех. Оттогаш беа додадени неколку анекси како Евротрансплант програмот за возрасни, кој ги доделува бубрезите од донори постари од 65 години на реципиенти со над 65 години старост. Заради константното рафинирање и усовршување системот ги постигна своите главни цели.

Клучни зборови: бубрежна трансплантација, доделување на органи, листа на чекање.

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