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CLINICAL, IMMUNOLOGICAL AND ETHICAL ASPECTS OF SELECTING A RECIPIENT FOR CADAVER KIDNEY TRANSPLANTATION

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The decision to choose a particular patient for kidney transplantation is made through two consecutive decisions: decision to include the patient on the waiting list and decision to select a patient competitively among several candidates for transplant. Both decisions are taken amidst many competing priorities and require a multidisciplinary approach. This paper provides comparative analysis of the principles of maintaining a waitlist and selecting a donor–recipient pair in Russia, Europe (Eurotransplant) and the USA (UNOS). *Donor–recipient pair is selected* based on the traditional hierarchical scheme of decision rules. Unlike Eurotransplant and UNOS, there are no uniform standards in Russia for assessing the quality of a donor organ. The widespread and largely vague "old for old" principle should be harmoniously fitted into the general outline of donor kidney distribution. The second difference in the national distribution system of donor kidneys is the choice in favor of a candidate with a lesser degree of sensitization. With high frequency of positive cross-test, this principle, in a synergistic manner, greatly reduces the availability of transplantation for highly sensitized candidates. The quality of donor organ and unconditional priority on highly sensitized candidates are the conceptual fundamental principles of organ distribution in the US and Europe. Under donor kidney shortage, selecting a recipient is always competitive. The choice of a candidate can be based on a patient-oriented approach (a choice in favor of the candidate whose transplantation will most likely reduce the risk of death; for example, an "emergency" waiting list) or an alternative – a utilitarian approach (choosing the candidate with the longest predictable life expectancy). However, radical commitment to one of these approaches inevitably reduces availability of kidney transplantation for a specific category of patients. For a justified choice of recipient, it is necessary to correlate such factors as comorbidity, waiting time, age, histocompatibility and quality of donor kidney. This would achieve a shaky balance between utilitarian approach and patient-oriented approach. The principles of creating a waiting list and a system for efficient distribution of donor organs practiced by foreign organizations cannot be simply copied and reproduced in Russia. It is necessary to adapt and validate such principles for the local patient population. The objective difficulties of such an analysis dictate the need to address it on a national scale. This would ensure equitable distribution of donor organs to all patients in need and obtain the best transplant results. Moreover, this would make it possible to achieve the full potential of donor organs. *Conclusions*. The situation in transplantological and nephrological care in Russia is gradually changing. This determines the need to adapt and standardize approaches to allocation of cadaveric donor kidneys in order to ensure equal access to transplantation for different patients and fullest realization of their potential. Removing organ distribution from the area of responsibility of local coordination councils, introducing a unified policy for distribution of donor organs and choosing a specific recipient will reduce the subjectivity of decisions and, possibly, improve transplantation results.

Keywords: kidney transplantation, waiting list, donor, recipient, comorbidity, histocompatibility, organ distribution.

According to the Declaration of Istanbul [1] organ transplantation, being one of the miracles of the twentieth century and a radiant symbol of human solidarity, continues saving and improving the lives of hundreds of thousands of patients throughout the world. It is generally accepted that kidney allotransplantation (ATP) is the optimal method of renal replacement therapy (RRT). Large studies have actually confirmed that the RRT method provides full medical and social rehabilitation for the patients as well as improved quality of life [2] and, most importantly, ensures the highest survival rate among patients with chronic kidney disease (CKD) [3–5]. This is true for the overall population of patients with CKD, however a practicing physician inevitably encounters the need to use the top-down approach, i.e. to determine the optimal RRT method for the specific patient. We will not discuss the advantages and drawbacks of hemodialysis or peritoneal dialysis and will concentrate on the approaches of patient selection for kidney transplantation, devoting a special attention to

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aspects relevant for our country. As it has been truly said in the European clinical recommendations on best clinical practices in examination and follow-up for donors and recipients for donor kidney transplantations [6], "… patient care after kidney transplant requires special knowledge in such areas of medicine as nephrology, immunology, pharmacology, endocrinology, communicable diseases and cardiology". On the one hand, this indicates the need of a multidisciplinary approach to management of candidates for transplantation and kidney transplant recipients; on the other hand – a potential possibility of a large number of contradicting and competing priorities present.

The choice in favour of ATP is implemented in the form of two subsequent decisions: including the patient into the waiting list and selection of the donor-recipient pair by means of determining a particular candidate for transplantation. We believe that the second decision is a harder one to make.

In Russia in routine clinical practice for kidney transplant, apart from the blood group, incongruity by three pairs of human leucocyte antigens (HLA) – first (HLA-A, -B) and second (HLA-DR) classes – are taken into account, namely, the number of the donor's antigens which are absent in the recipient [7] (with priority importance assigned to a minimum number of incongruities/mismatches by DR locus antigens). As practically each organ transplant center in our country has a small self-contained waiting list, opportunities for choosing an ideal candidate, taking into account tissue compatibility, are significantly limited. As a result in the majority of the cases the physician gets a list of patients who are equal from the point of view of tissue compatibility (equal number of HLA incongruities). There is no doubt that during the choice of a candidate for transplantation the physician is guided exclusively by humanistic intentions. At the same time, this choice is not quite as unambiguous as it might seem at first sight, and inevitably creates an ethical dilemma.

By the end of 2016 5050 patients have been included into the waiting list for kidney transplantation. During the year 2017 1175 kidney transplantations have been performed and 1925 patients have been added to the waiting list. Thus, taking into account those patients who had died or had been excluded for various reasons, by the end of 2017 the list contained already 5531 patients. It is clear that under conditions of such a shortage the choice of recipient is always competitive.

The choice of a recipient may be based on one of the two approaches. The first approach is patient-oriented. The main principle is decreasing the risk of death *at the moment of transplantation*. In order to implement this project the risk of death after ATP is related to the risk of death in case dialysis treatment is continued. The patient who has a higher *relative* risk of death is chosen as a recipient. According to this principle, for example, transplantation is performed for a patient who has been on the waiting list for a longer period of time. At the same time, as it has been shown [9], increasing the waiting time leads to the deterioration of the comorbid background. Apart from that, in accordance with this principle a so-called 'emergency waiting list' is formed (a typical example may be patients with exhausted possibilities of vascular access forming and impossibility of RRT conversion to peritoneal dialysis). In case of a favourable transplantation result the patient's lifespan may be quite long, while continuing hemodialysis treatment is related to a high risk of rapid death. Thus, transplantation enables to decrease manifold the risk of death, while a stable patient with a good functional arteriovenous fistula will gain significantly less benefit from ATP.

The patient-oriented approach facilitates a decrease in mortality for patients receiving dialysis (naturally among patients in the waiting list) as increased risk of death increases proportionally the likelihood of transplantation. However increased probability of transplantation along with increased risk of death is not monotonous: the patient may be excluded from the waiting list if the risk of transplantation exceeds the risk of death while receiving dialysis. Nevertheless, taking into account the competition for each donor organ, this approach inevitably affects also the other patients in the waiting list. As a result the average waiting time is increased for all the remaining candidates as a candidate who had been waiting for a long time will have a priority before a candidate with a shorter waiting time. This naturally facilitates a decrease in the life expectation for the other patients, as well as a decrease of the overall survival for the recipients after ATP (as this approach leads to an accumulation of a pool of recipients with lower life expectation). A positive aspect in this approach is a significant increase in the availability of transplantation for patients with burdened comorbid background. However at the same time the likelihood of transplantation is decreased in patients with a better comorbid background (this probability increases with the increase of time in the waiting list). The overall principle of this approach can be expressed by the words 'transplantation as a means of saving life'.

The other approach, an alternative one, may be described as utilitarian. According to it the preference ifs given to the candidate who has the longest predicted life expectation. This facilitates an increase in the overall survival of the recipients as well as a decrease of the overall time of waiting for transplantation. At the same time, this approach significantly decreases the probability of transplantation for patients with low predicted life expectation (as they are likely to not live long enough for transplantation or be excluded from the waiting list due to a deterioriation of the comorbid background) and may also increase the mortality among patients receiving dialysis (due to accumulation of a pool of patients in a worse condition, while patients in a better condition

will receive the transplant). The overall principle of this approach can be expressed by the words 'ensuring a maximally effective use of the donor organs from an utilitarian point of view'.

Thus, in practice a physician often faces the choice between performing transplantation for a patient with a higher risk of death, thereby somewhat worsening the prognosis for a patient with a lesser risk. Or the opposite: to give the preference with a higher predicted life expectation, therefore significantly increasing the risk of death for the patient in a worse condition. Radical commitment to either one of these alternative methods will inevitably decrease access to transplantation for a certain category of patients.

Under conditions of donor organ deficit such a dilemma will inevitably arise. It is clear that a compromise between these approaches is necessary in order to ensure a shaky balance between two ethical principles: potential benefit for the candidate's health and equity in organ distribution. Let us have a look at the experience of our international colleagues – large donor organ distribution systems such as Eurotransplant – ET (Europe) and United Network for Organ Sharing – UNOS (USA).

The system of donor organ distribution at ET is implemented by means of two programmes: Eurotransplant kidney allocation system (ETKAS) – kidneys from donors aged below 65 years old – and Eurotransplant Senior Program (ESP) – kidneys from donors aged 65+ [10]. Under the ETKAS protocol the patients are graded by blood group compatibility (according to the appropriate schemes) taking into account the following criteria: sensitization level (panel-reactive antibody – PRA), tissue compatibility (HLA-A, -B, -DR), time on the waiting list, HLA-mismatch probability and region of retrieval. This algorithm is intended primarily to ensure optimal immune compatibility of the donor (post mortem) and the recipient, at the same time it takes into account the time of waiting for transplantation.

The ESP protocol is used primarily in order to decrease conservation time and optimize the use of 'aged' donor organs. The organs are distributed sequentially at the local, regional and national level, not taking into account the donor's HLA phenotype among non-immunized recipients aged 65+ and ranged on the basis of urgency and waiting time. Immunized patients (those with previously existing anti-HLA antibodies) are included into the distribution according to the acceptable mismatch programme which permits transplantation from other groups. Transplantation through the EKTAS and ESP systems, according to ET policy, envisages transplantation exclusively when the donor's and recipient's blood groups match by the AB0 system.

Thus, the 'old for old' concept has not only been successfully implemented but also harmoniously introduced into the general framework of donor kidney distribution. This, on the one hand, increased the access to transplantation for elderly patients, and on the other hand, facilitated increasing the possibility for a young recipient to get an organ from a young donor. Short-term results after introducing the ESP protocol (in 1999) were quite promising due to significantly decreased conservation time (owing to priority distribution of the organs through this programme at the local level) [11]. Long-term results proved that the goal of the program had been achieved: the access to transplantation for elderly people has been increased, the waiting time for transplantation and the length of the conservation time have been decreased, the frequency of delayed renal graft function has been decreased. At the same time the frequency of rejection episode crises has somewhat increased and the graft survival has decreased as compared to recipients in the same age group who had received kidneys from younger donors [12]. Nevertheless survival rates among recipient were higher than survival rates among patients of the same age group from the waiting list [13, 14].

Thus, the key criteria for donor kidneys in ET are the donor's age and the candidates' sensitization. These primarily determine the choice of the protocol according to which the recipient will be selected.

In the USA the system of donor organ distribution with a common waiting list was introduced in 1977. One of the main criteria for recipient selection was the length of dialysis. An increased need in donor organs led to the need to use expanded criteria donors (ECDs). These included donors aged 60 and above, as well as donors aged 50–59 with at least one of the following criteria: serum creatinine over 1.5 mg/dl, death due to cerebrovascular causes or pre-existing arterial hypertension. Grafts received from such donors had over 70% higher risk of function loss [15]. At the same time the ratio of grafts obtained from ECDs in 2005 amounted to 17% of all post mortem donors [16]. When being included into the waiting list the patient made a choice regarding the possibility of receiving a kidney transplant from an ECD. Kidneys obtained from ECDs were distributed among patients who had agreed to participate in this programme in the following order: patients with no HLA mismatch at the national level, all other patients at the local, regional and national level taking into account the length of waiting time but not HLA compatibility [17].

The purpose here was a desire to decrease the time of waiting for a transplant. As large studies have shown, elderly patients had a low life expectancy and high risk of death with a functioning graft. At the same time younger patients with longer life expectancy after transplantation 'outlasted' the period of the graft's functioning and returned to dialysis and waiting for second-set grafting [18]. This enhanced the shortage of donor organs. A need arose to optimize the donor organ allocation system.

The 2008 American National Kidney Transplantation Concept [19], apart from HLA compatibility, was based on three main criteria: dialysis duration, panel-reactive

antibody (PRA) indicator and the life years from transplant (LYFT) ratio. The implementation of LYFT as an estimate indicator became a conceptual component of the evolution of the allocation system. LYFT is determined as the difference in life expectancy between two alternative options of the course of events, in one of which the patient will receive kidney transplant at the moment *from a specific donor* (total life expectancy with functioning graft, as well as after the loss of its function and resuming dialysis treatment), and in the other one – the patient continued dialysis treatment. Another important innovation was that while calculating this ratio the quality of life was indirectly taken into account: during calculation of life expectancy during dialysis treatment (in both options for the course of events) a reduction factor was applied (0.8) [20].

Changes also took place in the system of donor organ quality assessment. A binary classification (standard donors / donors with expanded criteria) has been replaced by a continuous scale. Donor kidneys were ranged in accordance with the kidney donor risk index (KDRI) [21] that indirectly reflected the potential of their functioning duration. This index, among other criteria, also included HLA compatibility. The allocation of donor kidneys with the highest expected functioning duration is influenced to a larger extent by the LYFT indicator (80%) and to a lesser extent (20%) by the dialysis duration as well as by PRA. The priority of the factors changes linearly along with deterioration of the donor kidney quality. Donor kidneys with the shortest expected functioning duration period are allocated only taking into account the dialysis duration and PRA [22]. Thus, candidates with the highest life expectancy received a priority in the allocation of kidneys with the highest potential survival. Patients who had been on the waiting list and receiving dialysis, on the other hand, received a priority in the allocation of kidneys with a shorter expected functioning duration. As a result transplantation availability for both patient categories has been improved.

The main arguments expressed by critics of the currently existing system of organ allocation were its complexity as well as low access to transplantation for highly sensitized patients. Also the LYFT calculation concept has been criticized. Despite the elegance of theoretical constructions and the information value of this assessment which has been proved during development, the experience of its use has shown insufficient precision of the prognosis. This has been related to a limited number of predictors that are used in the calculations [23]. For example, in the LYFT calculations the risk of cardiovascular events is not included (though such a possibility has been viewed in the course of developing the calculation method for this indicator [20]). At the same time it is known that cardiovascular diseases are the main cause of death for patients with stage 5 CKD [4, 5]. Kidney transplant recipients also have a higher risk of death from cardiovascular diseases than the general population rates [24] (though to a lesser degree than for patients receiving dialysis) [4, 25–27]. Thus, two candidates comparable by criteria included in the LYFT calculations may have significantly different prognoses.

The next stage of developing the allocation system in the USA towards a more comprehensive use of donor kidneys became the abandoning of LYFT and KDRI in favour of calculating a significantly more simple indicator – the expected post transplant survival (EPTS) rate. At the same time the quality of donor kidneys was evaluated by a new index – the kidney donor profile index (KDPI) [28, 29].

In the course of KDPI calculation the donors' age, height, weight, ethnic background are taken into account, as well as arterial hypertension and diabetes in the medical history, the cause of death, the blood serum creatinine level and hepatitis C status. In the course of EPTS calculation the recipient's age, diabetes status, previous organ transplantations and dialysis duration are taken into account.

The algorithm of recipient selection is carried out according to the traditional hierarchic scheme of decision functions. The initial link here is the donor organ quality – KDPI: on the basis of this score the kidneys are allocated to one of four categories, each of which has its own sequence of recipient choice. This system has two key principles. The first one is that the EPTS rate is calculated only for the best quality kidney allocation (for KDPI ≤20%). Thus, equity in the access to transplantation is assured.

The other key principle is an uncompromised priority for highly sensitized candidates (PRA 98–100%) and candidates with no HLA mismatches at the A-, B- и DRB1 HLA loci (this principle is observed for the allocation of kidneys with any KDPI rate) [18, 20, 30].

During kidney allocation the candidates are ranged in accordance with the number of points received for dialysis duration, PRA rate, compatibility by HLA-DRB1 locus. Additional points are allocated to children and patients who have become donors while alive. Same as in the previous system of kidney allocation, candidates for simultaneous transplantation (kidney and an extrarenal organ) have a priority.

An important feature of this system is a possibility for transplantation of cadaver kidneys to candidates from other groups with no HLA mismatches.

Implementation of the new system of donor organ distribution in 2014 has led to a small but statistically significant increase in the conservation length (from 15.8 to 16.8 hours), decrease of the average age of the recipients (from 55 to 52 years), increased correlation between the age of the donor and the recipient (from 0.35 to 0.38), decreased proportion of recipients without HLA mismatches (from 8.5 to 4.5%), decreased proportion of recipients above age 30 (from 19.4% to 15.0%). This led

to a significant increase in the proportion of recipients with PRA 100% (from 1.0% to 10.3%) [31]. At the same time the number of recipients below age 40 increased by 81.7%, and the number of recipients aged over 65 who received transplants with KDPI ≤20% decreased by 65.8% [32].

The long-term results of implementing this system are yet to be evaluated: it is not known how the survival of the recipients or of the transplants will change, as well as the proportion of recipients who die with a functioning transplant. However it is one of the most well-reasoned and balanced systems of donor organ distribution in the world.

DEVELOPMENT PROSPECTS FOR THE SYSTEM OF CADAVER DONOR KIDNEY DISTRIBUTION IN RUSSIA

The Russian national recommendations regarding creation and management of the waiting list for cadaver organ transplants, as well as the algorithm for selecting an optimal donor-recipient pair [7, 33], are aimed at ensuring fair allocation of donor organs to all patients who are in need of such transplants and obtaining the best results after transplantation. According to this document, selection of the donor-recipient pair is carried out taking into account blood group compatibility by the AB0 system, emergency status, anthropometric parameters and the period of being on the waiting list.

Primary selection of the pair is carried out on the basis of the blood group (by the AB0 system) and the result of the cross-match lymphocyte test. At the second stage the patients are ranged by urgent status or need for immediate transplant of several organs (such patients have an absolute priority). At the third stage the choice of a recipient is performed on the basis of histocompatibility with a priority to a minimum number of mismatches in the DR locus. Later patient priority is determined by the 'presence of pre-existing antibodies'. At the same time, despite ET and UNOS principles, recipients who do not have (or have a low level of) pre-existing antibodies have an advantage over patients with pre-existing antibodies (or their high level). At the final stage the candidates are ranged by length of period in the waiting list (candidates who have been waiting for a longer time have a priority). According to the Russian policy cadaver kidneys are allocated only in case of blood group matching.

The main initial stage of donor organ distribution both in the USA (UNOS) and in Europe (ET) for non-sensitized patients is the quality of donor organs. While in Europe the basis is the donor's age, in the USA it is a comprehensive score. We consider the introduction of such a score (or at least a binary feature like in ET) to be an effective measure (probably the most relevant one at the current stage of kidney transplantation development in Russia) which will facilitate an increase in access to transplantation. Patients with diabetes, elderly patients, patients with burdened comorbid medical history should not be limited in access to transplantation. Equity is a basic ethical principle for any donor organ distribution system. On the other hand, it would ensure a most effective organ allocation, enabling to implement the donor kidney potential to a maximum. Patients with the longest predicted life expectancy should receive the best quality kidneys. This approach will ensure an optimal balance between patient-oriented and utilitarian approaches to distribution.

It is evident that in order to implement this approach it is necessary to develop a system of donor organ quality evaluation and a comprehensive assessment of the potential recipient's condition. Recent studies have shown that it can not be achieved by simple copying of the organ distribution system: for example, the effectiveness of the current organ distribution system which has been successfully implemented and is efficiently functioning in the USA may be doubtful in Europe [34].

The most important factors which influence the quality of a donor organ, *relevant for the donor pool in our country,* should be determined. Such factors may be: diabetes mellitus, arterial hypertension, the donor's age, functional condition of the kidneys, the donor's cause of death, type of donor (donor with palpitating heart / asystolic donor). In some cases patient history may be unavailable. Kidneys obtained from such donors may be attributed to a separate category. In this case assessing the quality of the kidneys may be carried out exclusively on the basis of instrumental and laboratory examination data. donor type, cause of death and age.

Assessment of the recipient's condition can present the most difficulties. First of all, prioritization of the recipients may be based either on calculating the predicted life expectancy or on the potential benefit from transplantation (EPTS and LYFT analogs). As a rule, such assessment may be obtained as a result of determining a regression equation which describes a dependency between a certain outcome and a set of predictors with optimal approximation. The set of predictors is determined by the biological significance of the evaluated characteristics and is limited, on the one hand, by the quality of assessing these indicators, and on the other hand – by their relevance for the population under examination.

Absence of contraindications for transplantation is not the only criterion which determines the need for kidney transplantation to a patient with stage 5 CKD (though it is the main one that determines its possibility). The second mandatory condition is confidence that transplantation will lead to increasing the predicted life expectancy or the quality of life. This may be achieved as a result, for example, of studying the connection of quantitative assessment of the comorbid background and the transplantation results in comparison with dialysis treatment and, most importantly, opportunities for using

it to make individual forecasts. Earlier it has been shown by us [9] that deterioration of the comorbid background as a result of prolonged waiting facilitates increased mortality among the recipients after transplantation. This leads to decreased expediency of kidney transplantation as it does not result in a significant improvement in the prognosis versus continuing dialysis treatment.

Calculation of the comorbid background is very important for individual risk assessment (the patient's interests) but also for the development of organ distribution policies (the interests of the supervisory authorities) and for the prioritization of the candidates (the transplantologist's interests). While during inclusion into the waiting list the decision may be made on the basis of a number of binary signs (for example, presence/absence of an infection process, malignant neoplasms or recent myocardial infarction), in order to compare the recipient's comorbid background with the donor organ quality evaluation in an ordinal or interval scale may be required (due to relativity of scales used for comorbid background assessment the possibility to measure the health condition by an absolute scale – a ratio scale – seems quite doubtful even on condition of assuring acceptable equidistance).

Predicted life expectancy calculation (EPTS analogue) seems to us to be a more illustrative and balanced assessment for patients *with a good prognosis*. Even though this assessment is clearly relative, it may have a discreet character (for example, less than 10 years, 10–20 years, over 20 years). At the same time, this may decrease the chances of transplantation for patients in a worse condition. In turn, a ratio showing potential benefit from transplantation (LYFT analogue) during short follow-up time will more likely favour *patients with more severe conditions* [20] for whom the *absolute* life expectancy will increase less compared to a significant *relative* increase of the life expectancy in case of transplantation compared to continuing dialylis treatment. This is due to the fact that patients with a shorter life expectancy achieve their LYFT potential soon after transplantation, while patients with a longer life expectancy achieve their LYFT potential at later stages (10–15 years later).

Patients with diabetes mellitus may be an example. It is known that recipients with diabetes have a significantly shorter life expectancy than patients without diabetes [3–5]. At the same time, younger patients with diabetes mellitus may get a dramatic benefit from kidney transplantation as compared to patients from the same age group without diabetes [18, 20]. This is due to an extremely high mortality among such patients receiving dialysis.

Another example may be patients who need prompt transplantation: their life expectancy after transplantation may be increased by several times as compared to the course of events if they remain on dialysis treatment. However due to the fact that the patients from both examples will have a generally relatively short predicted life expectancy, it would be advisable to perform transplantation of a kidney the functional potential of which will be used up sooner than that of better quality donor kidneys. For a fuller utilization of the donor kidney potential it is necessary to implement an evidence-based system of correlating the surrogate assessment of the patient's condition to the quality of organ which would significantly supplement the uncertain 'old for old' principle.

Thus, the quality of the donor organ should be a key aspect in distribution. For example, when the predicted life expectancy is below 10 years, the kidneys may be allocated taking into account the maximal benefit from transplantation, in case of longer life expectancy – taking into account post-transplantation survival.

Another factor that appears important to us is medical compliance assessment (cognitive disorders, lack of adherence to instructions received from treating physician, missing dialysis procedures, etc.). This factor should also be taken into account in determining candidate prioritization.

Currently we do not have a clear understanding as to how such factors as comorbid background, histocompatibility, waiting period and recipient's age should be introduced into the distribution scheme. We believe that at different times during the waiting period (here it is not the total period of being on the waiting list that should be taken into account but the total length of dialysis treatment) the priority of these factors changes, moreover, in a non-linear manner. Previously [9] we have received strong evidence in favour of this fact: the significance of comorbitity increases along with the increase of the dialysis treatment duration. It is quite possible that in case of long-term waiting the potential benefit from transplantation is significantly decreased even in case of a minimum number of HLA-mismatches. There is also other proof in favour of this assumption [35].

Additional complication is added also by the fact that a significant effect may be due to the interaction of different factors which may be non-linearly related to the outcome probability. For example it is evident that the risk of death for the patient gradually (and probably linearly) increases along with increased age and deterioration of the comorbid background. At the same time the comorbid background will deteriorate (and this means that the risk of death will increase) along with the increase of the waiting time faster in elderly patients as compared to younger ones [36]. Thus even these three factors (age, comorbid background and waiting time) result in a need to include their interaction with corresponding coefficients into the regression model. Adding such an important factor as the presence or absence of diabetes complicates the analysis even further (it is evident that deterioration of the comorbid background in patients with diabetes takes place at a faster rate than in

patients without diabetes). Nevertheless this problem may possibly still be solved. Analysis of the regression equation used to calculate the EPTS rate [37] shows that several predictors are represented by an interaction of different factors. At the same time, a large volume of primary data and the need for mandatory external validation of the model determine the need to solve this problem at the national level. We have been consistently working on this already for several years on the basis of a developed retrospective database. At the same time limited resources and volume of clinical material, as well as its local character indicated a certain bias in the assessment: its result (a draft scheme for donor-recipient pair selection) may be relevant only for our region.

Apart from this, an important aspect of the work which largely determines the opportunities for practical application of its results is the localization of PRA calculations as well as possibility for acceptable mismatches in sensitized recipients. Calculations may be based on the results for a local patient pool or on available data from open sources [38, 39] regarding antigen population frequency in the given region. Such assessments may also have a significant influence on determining priorities among the candidates.

Transplantation probability (not taking into account the comorbidity factor) is a random variable. An important factor which may theoretically influence the priority of the candidates may be the population frequency of antigens which constitute the phenotype and which are taken into account during selection of the pair. It is quite possible that candidates who have a rare HLA phenotype may wait for transplantation for a long time [40–42]. At the same time the waiting time may compensate the impact of this factor in case it is determined that after a certain waiting period the priority of HLA histocompatibility is decreased in favour of other clinical factors (for example the comorbid background).

A disadvantage of the Russian donor kidney distribution system is a lack of a unified waiting list which significantly hinders the choice of an optimal recipient from the point of view of tissue compatibility. Taking into account the territorial peculiarities of our country, the waiting list may be a general one which would unite the efforts of several transplantation centers (not only at the federal region level but by territorial principle). The probability of a center getting a donor organ (for a specific patient) would be determined first and foremost by the size of the local pool of transplantation candidates and would be limited by the possibility to perform a certain number of operations. At the same time the probability of transplantation being performed after receiving a donor kidney is determined by the quality of the waiting list maintenance (updated information about the candidate's condition). Apart from determining the organ distribution policy it is necessary to compare the impact of conservation duration on long-term survival for various quality grafts with the benefit that transplantation with a good immunological background may provide. It may possibly be justified only for candidates whose PRA values are close to 100%.

The fact that under the modern organ distribution system non-sensitized candidates have an advantage over sensitized ones definitely limits the accessibility to transplantation. This may be due to the fact that desensitization of the patients who have pre-existing anti-HLA antigens and are expecting cadaver kidney transplants is not a consistent practice. The results of transplantation in case of pre-existing antibodies may be improved by implementing a virtual cross-match procedure which would take into account the presence of common epitopes [43–45]. Determining acceptable mismatches may significantly improve the results of transplanting kidneys to sensitized candidates [46, 47].

CONCLUSION

Kidney transplantation undoubtedly remains the optimal renal replacement therapy method for the vast majority of the patients. The transplantology and nephrology care environment in our country is gradually changing. This determines the need to adapt and standardize the approaches to the distribution of kidneys obtained from cadaver donors in order to ensure equal access to transplantation for different patients and the maximum fulfillment of their potential. Withdrawing organ allocation from the area of responsibility of the local coordination committees, introducing a unified policy for donor organ distribution and choice of a particular recipient will enable to decrease the bias of the decisions made and possibly improve the transplantation results.

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