Preemptive kidney transplantation: ethical issues

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Summary. Preemptive kidney transplantation, as a treatment modality for end-stage renal disease, offers higher clinical advantages compared to maintenance dialysis. Nevertheless, preemptive transplantsations raises ethical concerns, particularly regarding medical resource allocation. From an ethical perspective, health care decisions should be focused on the patient’s needs. Nevertheless, a fair distribution model also requires the settlement of general policy decisions. The first part of the paper presents general ethical principles to be followed in organ allocation. The second part summarizes main advantages of preemptive transplantation in terms of clinical outcomes, survival (of both patients and grafts) and quality of life. The third section adds some suggestions for the fulfillment of general principles in the context of preemptive transplantation. The need to find an adequate balance of benefit (maximization of utility) and justice (fairness in organ allocation) is analyzed. A common set of rules for organ allocation should be adopted: fairness and transparency requires the prior definition of sound criteria for the allocation of scarce resources.

Key words: bioethics, organ transplantation, prevention.

Riassunto (Il trapianto “preemptive” di rene: aspetti di etica). Il trapianto preventivo di rene è un trattamento che può essere adottato in stadi avanzati di patologia renale e che offre vantaggi clinici rispetto alla dialisi. Tuttavia, il trapianto preventivo pone alcuni problemi di etica, specialmente per quanto riguarda l’allocazione delle risorse. Sotto il profilo dell’etica, le decisioni in ambito sanitario dovrebbero essere motivate innanzi tutto dal bene del singolo paziente. Tuttavia, un equo sistema distributivo impone di prendere anche decisioni sulla base di politiche sanitarie con valenza sociale. La prima parte dell’articolo enuncia alcuni principi generali di etica nell’allocazione di organi a scopo di trapianto. La seconda parte riassume i principali vantaggi del trapianto preventivo in termini di risultato clinico, sopravvivenza (sia del trapianto, sia del paziente) e di qualità della vita. Nella terza parte sono contenute alcune proposte per l’applicazione dei principi generali nel caso specifico del trapianto preventivo. Si analizza la necessità di individuare un adeguato bilanciamento tra benefici (massimizzazione dell’utilità) e giustizia (equità nell’allocazione degli organi). Si suggerisce l’adozione di criteri unificati e condivisi: l’equità e la trasparenza richiedono che siano definite a priori solide regole per l’allocazione di risorse limitate.

Parole chiave: bioetica, trapianto di organi, prevenzione.

GENERAL BIOETHICAL PRINCIPLES AND ORGAN TRANSPLANTATION ETHICS
Bioethical principles as a reference in decision making

Autonomy, beneficence and justice are the most known bioethical principles suggested for the decision-making [1]. Similar values, considered in different anthropological frameworks, have also been proposed. For example the personalistic approach formulates the principles as follows [2]:

- therapeutic principle (or beneficentiality). The well-being of each individual must be the primary goal of healthcare policies and interventions. Beneficentiality is also connected with the risk-benefit ratio and respect for the integrity of donor and recipient (primum non nocere). It is also related to prudence, the “mother, custodian, moderator” of all virtues.

“Prudence” derives from procul videns, or “farsightedness”: it is the recta ratio agibilium, that is to say reason as a guide for our behaviour;

- freedom and responsibility principle (or independence). It is associated with the need for a consent without coercion, expressed on the basis of precise and understandable information;

- sociality and solidarity principle (justice). It includes both justice in distribution (suum quique tribuere: to each his/her own), and in commutation (neminem laedere: do not harm anyone). This principle requires to: guarantee equal access, organise suitable services, counteract the trading of the human body and its parts, oppose to any other degeneration, promote a correct culture of donation.

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Specific criteria

The main ethical duties for organ transplantation can be summarized in the following criteria [3]:
- organs may be removed from the bodies of a deceased person if the consent required by law has been obtained during his/her life or if there are no reasons to believe that the deceased person would have objected to the removal;
- physicians determining the death of a potential organ donor should not be directly involved in organ removal from the donor and subsequent transplantation procedures;
- organs for transplantation should be removed preferably from bodies of deceased persons. Adult living person may donate organs, but in general such donors should be genetically related to the recipients;
- the human body and its parts cannot be the object of commercial transactions;
- the safeguarding of individuals is imperative: the risks for living donor and recipient must be reduced to a minimum; assistance must be up to the highest standards;
- the donor’s cadaver must be respected.

As regards the even more specific issue of organ allocation, the main criteria involved are associated with:
- selection of the sickest patient;
- selection of the patient most likely to benefit based on medical and other criteria;
- selection of the patient on the waiting list for the longest period;
- all patients on the waiting list should have an equal chance of selection.

Special circumstances might call for further criteria. For example serious emergencies may require a selection of patients on the basis of their importance for the well-being of others. This and other non-medical criteria raise important questions about the manner in which selection attributes are to be quantified and who is entitled so.

Nevertheless, emergency situations are not the case with preemptive transplantation.

The above criteria may be conflicting. This may happen in every situation, but is particularly likely in preemptive transplantation. Therefore, a sound ethical analysis is necessary not only to verify the consistency between facts and values, but also to help in the identification of a reasonable balance among conflicting values.

CLINICAL AND SCIENTIFIC DATA

The following data are by no means comprehensive: they are intended to provide examples by summing up results of a few studies published in literature. Generally speaking, their outcome converges in pointing towards the usefulness of preemptive kidney transplantation.

Preemptive transplant is advisable in advanced stages of the disease (stage V): in previous stages (III, IV) it is not advisable because patients can be expected to remain in those stages for several years, in acceptable health conditions [4].

The clinical advantages of preemptive kidney transplantation compared to dialysis, suspected for many years, became evident after the publication of several studies at the end of the Nineties.

In 1988 Asderakis et al. [5] analyzed data from 1463 consecutive first kidney transplants performed between January 1980 and December 1995 in a single centre. The 161 patients (11%) transplanted without prior dialysis were compared with the 1302 patients who received dialysis prior to being transplanted. The actuarial graft survival in the preemptive group at one, five and ten years was significantly higher than the respective values in the dialysis group. Within the living donor recipient cohort the survival advantage was even more striking.

In 1999 Wolfe et al. [6] conducted a longitudinal study of mortality in 228 522 patients who were receiving long-term dialysis for end-stage renal disease from 1991 to 1997. Of these patients, 41 164 were placed on a waiting list for transplantation, 23 275 of whom received a first cadaveric transplant. The authors showed a significant benefit in survival for transplanted patients compared to a control group of patients medically cleared for transplantation and placed on the waiting list. Survival advantages applied to all categories of patients by age, race and primary cause of renal disease.

More recently, Becker et al. [7] examined the impact of preemptive kidney transplantation on post-transplantation mortality and graft failure in 23 238 adults, receiving the organ from either a living or a deceased donor. Preemptive transplantation was performed in 14.4% of patients. The results showed that preemptive transplantation was associated with a lower relative risk of mortality.

In the same year Pérez-Flores et al. [8] compared the outcomes of 33 patients who received preemptive kidney transplantation from deceased donors with those of renal transplant in subjects who had undergone dialysis. The results showed that preemptive kidney transplantation is associated with lower delayed graft function. Even if 2-year graft and patient survival in the two groups were similar, the authors concluded that “preemptive deceased donor kidney transplantation is the treatment of choice for advanced chronic kidney disease”.

Similar results were obtained in the same year by Dębska-Śliżien et al. [9], who studied 15 preemptive grafts, constituting 11.5% of all kidney transplantations performed in their hospital in Gdańsk (Poland). The results showed that the incidence of delayed graft function (dialysis in the first week after transplantation) was significantly lower among preemptive recipients, although the two groups did not differ either in respect to occurrence of acute rejection episodes or graft and patient survival.

In 2007 Innocenti et al. [10] retrospectively analyzed 438 sequential solitary living donor kidney
transplants, 44% of whom were preemptive and 56% non-preemptive. Overall, the three-year patient survival was similar in the two groups, but delayed graft function was more frequent in the non-preemptive group.

Many studies also demonstrated that pretransplant dialysis is a significant risk factor for graft loss and posttransplant death and that there is a direct association between the duration of pretransplant dialysis and negative outcomes following transplantation [11]. Moreover, outcomes for recipients of living donor transplants are consistently superior to recipients of deceased donor transplants [12].

**ANALYSIS AND SUGGESTIONS**

Data from the literature show that transplant before dialysis leads to better results compared to transplant performed after dialysis.

Moreover, although this is a simplification, the above mentioned data on the whole allow us to draw a relevant conclusion: the survival and clinical advantages of preemptive kidney transplantation are evident in many countries, which differ in healthcare systems and patients’ demography. The results apply to all categories of patients regardless of age, population, and primary cause of renal disease.

Clinical data, therefore, point to the usefulness of preemptive transplant.

**The “tragedy of commons”**

Preemptive transplant involves difficult choices as regards organs’ allocation. The situation, though different, shows some similarities with the question known as the “tragedy of commons”. The word “common” here derives from “common lands”, that is to say those plots of land which, until the 17th century, were made available in England for collective use by the rural population. Today the word “commons” is used when referring to a wide range of goods and services necessary for survival and collective well-being, including for example natural resources.

Organ transplantation is first and foremost an individual issue: the organ taken comes from a human being and is donated to another human being. In this respect it is not a “common”. However, there is also a social dimension involved: indeed, it is necessary to establish allocation criteria because the number of candidates for transplant is greater than that of the organs available.

It seems fair to say, therefore, that also as regards organs’ allocation there is a “tragedy of commons” similar to the one described in 1968 by Garrett Hardin in a well-known article published in 1968 by *Science* [13]. Hardin made reference to conflicts between individual interest in the use of common property, highlighting that the common goods lose value as a consequence of conflicting individual interests between many people. Central to Hardin’s article is a metaphor of herders sharing a common parcel of land, on which they are all entitled to let their animals graze. Hardin shows that it is in each herder’s interest to put as many animals as possible onto the land, even if the commons are damaged as a result: the herder receives all of the benefits from the additional animals, while the damage to the commons is shared by the entire group. If all herders make this individually rational decision, however, the commons are destroyed and all herders suffer.

In the case of organ allocation the situation is different not only because of the extremely personal nature of the asset (human organ) on which there is competition, but also because the allocation involves an all/nothing choice (only one individual receives the goods, which cannot therefore be used partially by several people). In any case, some of the remarks by Hardin may be valid, some time later, also for the issue of transplants. For example, as regards the remarks which will be made later about the organisation of the transplant management system, it is significant to note that Hardin attributes primary importance to the organisation of national coordination networks. Hardin, in fact, advises to “replace the disorder” caused by the aggregation of individual interests with a “legitimate authority which is able to encourage users” to adopt sustainable behaviours by means of formal rules.

**Specific problems**

Preemptive transplantation is a therapeutic opportunity. Not all therapeutic opportunities are ethically acceptable. Nevertheless, an exclusion a priori would be unacceptable.

Therefore, it is essential to regulate clearly the whole system, in order to guarantee control, traceability, equity, efficiency and well-grounded choices. These requirements can be satisfied only with the entry of patients in waiting lists. Nevertheless, waiting lists may raise relevant problems both practical and ethical. Consequently, great attention should be paid in defining algorithms for the selection of patients. Algorithms should be implemented at the national level, in order to promote equity in the system. The adoption of different algorithms, indeed, may cause disparities between candidates for preemptive transplantation and candidates already in dialysis. For example, this might happen if a patient is registered in a list where the algorithm privileges the time spent in the list, and another patient is registered where the algorithm privileges efficacy of the results. In the first case patients already in dialysis are favoured, while in the second case preemptive transplantations are favoured.

The option of living donors deserves a special attention. Studies mentioned in section two, and other studies, indicate clearly a clinical advantage when organs come from living donors as opposed to cadavers. Nevertheless, in an ethical perspective, the living donor should not be regarded as a preferential option. This requirement is clearly set by codes, declarations, guidelines and other documents. For
example according to the Convention on Human Rights and Biomedicine: “Removal of organs or tissue from a living person for transplantation purposes may be carried out solely for the therapeutic benefit of the recipient and where there is no suitable organ or tissue available from a deceased person and no other alternative therapeutic method of comparable effectiveness” [14].

The issue of compliance (that is patient’s correct following of medical advices) should also not be underestimated. Data in the literature suggest that patients who have not been subject to the tribulations of dialysis tend to be less compliant than those who received the transplant after having undergone dialysis. Failure to comply may jeopardise the course of the disease, thus leading to a “waste” of organs which could have been allocated differently.

**Utility, justice and the double effect**

Among the general criteria for the attribution of organs to the best-matched recipient there are: biological compatibility, size of the organ and of the body, age, clinical urgency, time spent in the waiting list, geographical distance from donor to recipient, and others.

Two key ethical criteria are decisive in choices for organ allocation: benefit (maximization of utility) and justice (fairness in distribution).

Benefit is a foundation in clinical practice, in bioethics and in deontology. Nevertheless, benefit should not be the only criteria to be considered: a purely utilitarian approach is unethical. Social utility (maximization of utility for the community) is a criterion not acceptable for organ allocation. Medical utility is a proper criterion, although it should be considered together with other values. Assessing the medical utility is a difficult task, since parameters difficult to quantify should be considered (patient survival, graft survival, clinical parameters, quality of life, psychological conditions, and many others).

Justice should also be considered. The “best” algorithm in terms of benefit might be unfair. Indeed, the evaluation of the amount of good done is not sufficient to fulfil ethical requirements: the pattern of distribution of the good should also be taken into account. Justice can be seen from different perspectives. The main perspective is egalitarian: a pattern of distribution is considered fair if it gives people opportunities for equality of outcome. In clinical practice this means an effort to give those who are the worst the same opportunities, as far as possible, to be as healthy as other people. Nevertheless, since justice and utility should be considered together, this does not mean that very sick patients consume all the resources.

Three factors seem particularly important in order to balance utility and justice: present need, urgency and need over a lifetime:

- the present medical status of the recipient should be taken into account. Justice interpreted in an egalitarian perspective requires that people should have an opportunity to be as well as others, as far as possible. In general this means that those who are the sickest or otherwise worst-off deserve first consideration. Nevertheless, this is not the most important factor in decisions on kidney transplantation, because patients can usually be maintained indefinitely on dialysis;
- medical urgency, in the case of transplantation is usually interpreted in terms of expected duration of life. In the case of kidney transplantation other parameters must be considered. Some patients on the waiting list may need a transplantation urgently even if they are not among the sickest category of patients. Therefore, two main kinds of urgency should be considered: expected imminent decline and likelihood of finding a suitable organ in the future;
- need over a lifetime is another concept that should be considered. Some patients do not have an extraordinary present need or a great urgency in getting transplanted, but it should be considered that such a postponement may oblige them to accept a low quality of life. In this context factors such as waiting time are particularly important.

As regards the assessment of organ allocation, the relevant principle seems to be the one which ethics and philosophy usually define as that of “double effect”. The double effect principle refers to situations where an action characterised by a positive aim also has one or more unwanted negative outcomes. The principle therefore provides useful indications to determine whether, from an ethical perspective, it may be acceptable to act in search of something good while being aware that the action will also involve something bad. As for the case in point, the “good” is the transplant which allows a patient to avoid dialysis (in line with a utilitarian concept), and the “bad” result consists in the fact that another patient, who is being dialysed and on a waiting list, will be forced to wait longer (thus partially transgressing the justice principle).

According to a widely shared approach to the double effect principle, the actions aimed at something good which also involve negative consequences are acceptable from an ethical perspective provided that the following four requirements are abided by [15]:

- the main aim of the action and the action itself must be good;
- the negative outcome must not be intentionally searched for;
- the negative consequences must not be the goal of the action, nor must the good outcome be a direct consequence by cause-effect of the negative result;
- the positive aim which is being pursued must be proportionate to the negative consequences, in other words the former must exceed the latter.

**GENERAL REMARKS**

The “Explanatory report” of the “Additional protocol to the Convention on Human Rights and
Biomedicine, on transplantation of organs and tissues of human origin” [16], stresses the importance of adequately defining allocation criteria, acknowledging that “organs and tissues shall have to be allocated following medical criteria” (paragraph 37, related to article 3 of the Convention [14]).

Resources includes both organ and services. Responsibility for the provision of the infrastructural resources underlying clinical transplantation rests with politicians, particularly when the amount of resources to be partitioned between various necessities, both medical and non-medical, is limited. This may create considerable tension and require difficult trade-offs, especially in situations in which many potentially interested people are excluded either de jure or de facto from decision-making processes.

The choice of common rules and operating criteria is essential. Nevertheless, a fair process requires that a decision-making extends beyond medical criteria and political considerations. Medical benefit and justice are absolutely essential criteria for organ allocation, but other ethical values should also be taken into account. Bioethics experts will need to support the selection of reference principles and the possible methods to implement them.

Is it necessary to consider, however, that the primary reference value is always solidarity. Personalism, by regarding the person as a fundamental value, emphasizes solidarity and invites to promote the collective good by safeguarding and giving value to the well-being of each individual [17].

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