

NDT Perspectives

Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP

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ABSTRACT

This position statement brings up guidance on pre-emptive kidney transplantation from living donors. The provided guidance is based on a systematic review of the literature.

Keywords: transplantation, living donation, pre-emptive, end stage renal failure, dialysis, guideline

FIRST STATEMENT

We recommend that programmes for pre-emptive kidney transplantation with living donor kidneys should be stimulated (1D)

Advice for clinical practice

Awareness programmes and early patient education on the possibility of pre-emptive living donation during the process of

modality selection can enhance shared decision making when this becomes necessary.

RATIONALE

Why this question?

There is general consensus that, for suitable candidates, transplantation improves quality of life, and probably also longevity. However, due to organ shortage, there is a waiting time on dialysis for most patients. There is some concern that during this waiting time on dialysis, there is accumulation of comorbidities associated with chronic renal failure and dialysis. Living donation can expand the available kidney donor pool, and creates the possibility for pre-emptive, i.e. before initiation of chronic dialysis, transplantation in a fair way. Pre-emptive transplantation has in addition the potential for the patient to avoid the need for creation of an arteriovenous fistula or peritoneal dialysis catheter surgery. Pre-emptive transplantation would also be cost-effective as the costs of dialysis are higher than those of the follow-up of transplanted patients. On the

other hand, there might be concerns that pre-emptive transplantation might result in an increased risk of graft loss from rejection because these patients do not present the immunosuppressive effects of uraemia and because the lack of experience with dialysis might negatively affect patient adherence. In addition, living donation, especially when pre-emptive, always raises the concern for the safety of the donor.

What did we find?

We used the PICO and search strategy as defined in Appendixes 1 and 2. We did not retrieve any randomized controlled trial comparing pre-emptive transplantation with post-dialysis transplantation. Only observational data, mainly coming from single centre or regional registries, are available.

We retrieved 29 retrospective observational cohort studies (26 published articles and 3 abstracts) performed after 1990 providing data on aspects of pre-emptive living donation [1–29] (Figure 1). We considered that older cohorts would be outdated and would not provide relevant data.

Twenty-two papers report mostly patients transplanted between 1990 and 2000, while seven report only on patients transplanted after 2000. Fifteen studies came from the USA, five from Europe and nine from other regions.

Twenty-one papers report on adult recipients and eight on paediatric recipients. In 13 articles, the donors were either living or deceased, in 10 they were only living donors and in 2 only deceased donors. For three studies, it was unclear what type of donors was actually included.

Data on patient survival, graft survival and acute rejection were provided in 19/29, 23/29 and 13/29, respectively, whereas risk for infection and malignancy was reported only in 2/29 (see Supplementary data, Appendix 3).

Patient survival, graft survival and acute rejection rate were better in pre-emptive versus after start of dialysis in 9 out of 19 (equivalent in 4), 13 out of 23 (equivalent in 2) and 10 out of 13 (equivalent in 2) papers reporting this outcome in adults, respectively. In children, patient survival was better in pre-emptive versus after start of dialysis in the only article reporting this outcome, graft survival was better [25, 26] in two out of four (equivalent in one [16] and worse in one [29]) and acute rejection rates were equivalent in two out of two papers reporting this outcome.

Some have shown a stepwise dose-dependent decrease in patient and graft survival with increasing duration of dialysis [6]. However, dialysis periods shorter than 1 year seem to have no significant impact on either patient or graft survival [13].

Occurrence of delayed graft function (DGF) was reported in four articles [4, 11, 12, 19]. The reported percentages of DGF varied between 2% [11] and 3.7% [12] with pre-emptive transplantation, versus 4% [11] and 9.7% [12] in patients transplanted after the start of dialysis.

All papers had a high risk for selection bias. This is visualized in the risk of bias grid (Figure 2) by the fact that it was uncertain whether pre-emptive patients were representative of the overall cohort, and whether non-pre-emptive patients were drawn from the same cohort. Further, there was uncertainty in most

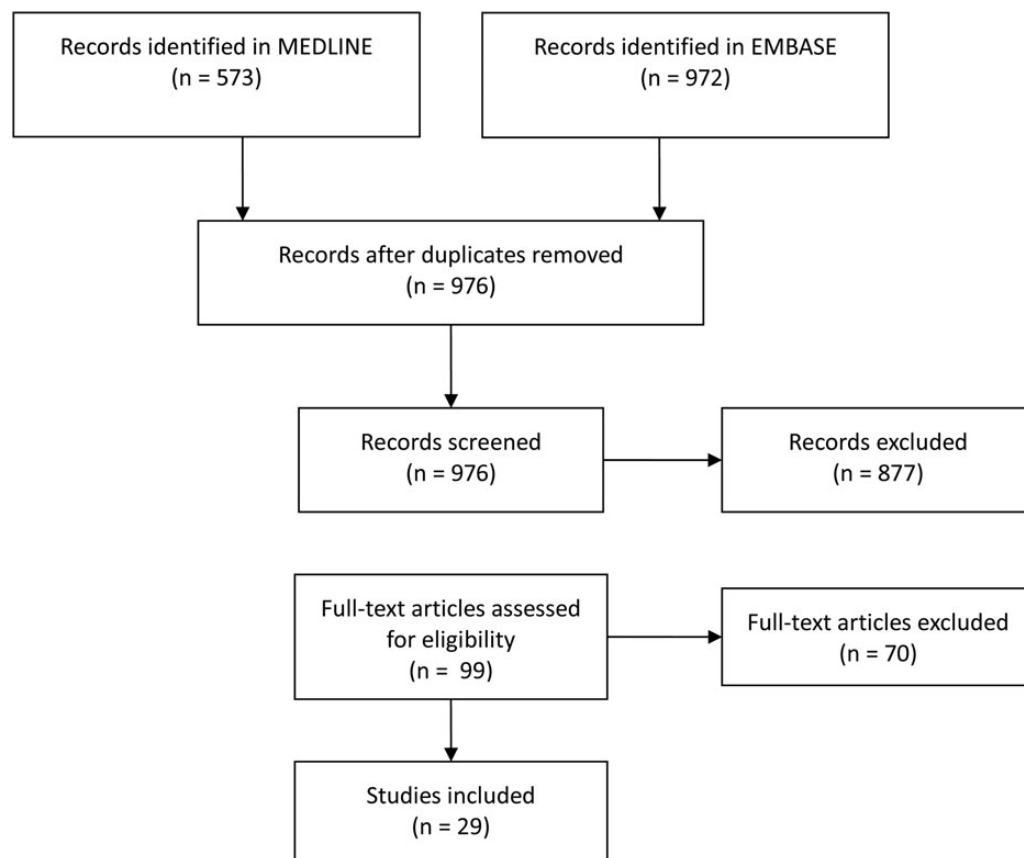


FIGURE 1: Flow diagram of study selection process.

Author year	Representative exposed cohort	non exposed cohort drawn from same community	adequate ascertainment of exposure	demonstration outcome of interest not present at start of study	adequate control for most crucial confounders	adequate control for additional confounders	adequate assessment of outcome	follow up long enough for outcomes to occur	adequate cohort follow-up
Jung 2010 [1]	0	0	+	+	-	-	+	+	+
Kasike 2002 [2]	0	0	+	+	+	+	+	+	0
Katz 1991 [3]	0	0	+	+	-	-	-	+	+
Mange 2001 [4]	0	0	+	+	0	0	+	+	+
Meier-Kriesche 2000 [5]	0	0	+	+	0	0	+	+	+
Meier-Kriesche 2002 [6]	0	0	+	+	0	0	+	+	+
Milton 2008 [7]	0	0	+	+	0	0	+	+	+
Verbese 2012 [8]	0	0	+	+	0	0	+	0	0
Wiseman 2013 [9]	0	0	+	+	-	-	+	+	+
Yoo 2009 [10]	0	0	+	+	-	-	+	+	+
Gill 2004 [11]	0	0	+	+	-	-	+	+	+
Innocenti 2007 [12]	0	0	+	+	0	0	0	+	-
Goldfarb-Rumyantzev 2005 [13]	0	0	+	+	+	0	+	+	+
Goldfarb-Rumyantzev 2006 [14]	0	0	+	+	-	+	+	+	+
Johnston 2013 [15]	0	0	+	+	+	+	+	+	+
Harada 2001 [16]	0	0	+	+	-	-	+	+	+
Heidotting 2011 [17]	0	0	+	+	-	-	+	+	+
Langlois 2000 [18]	0	0	+	+	+	-	+	+	+
Joo 2007 [19]	0	0	+	+	-	0	+	0	0
Ishikawa 2008 [20]	-	0	+	+	-	-	+	+	+
John 1998 [21]	-	0	+	+	-	-	+	+	+
Abou Ayache 2005 [22]	0	0	+	+	-	-	+	+	+
Becker 2006 [23]	0	0	+	+	+	+	+	+	+
Berthou 1996 [24]	0	0	+	+	-	-	+	+	+
Butani 2011 [25]	0	0	+	+	-	-	0	+	+
Cransberg 2006 [26]	0	0	+	+	+	-	+	+	+
Cransberg 2000 [27]	0	0	+	+	-	-	+	+	+
Duzova 2009 [28]	0	0	+	+	-	-	-	+	+
Flom 1992 [29]	0	0	+	+	-	-	+	+	+

FIGURE 2: Risk of bias table.

studies as to whether essential and additional confounders were taken into account, also reflecting the potential presence of unadjusted imbalances between the pre-emptively and non-pre-emptively transplanted group.

How did we translate the evidence into the statement?

Several registry analyses (USRDS, ANZDATA and others) have reported better patient and graft survival in recipients with a pre-emptive transplantation when compared with those receiving a transplant after dialysis [2, 7, 13, 30].

However, these observational registry-based studies carry by nature important limitations. Pre-emptive kidney recipients are not necessarily representative of the overall transplanted

patients, which should be kept in mind in the interpretation of the results. The risk of bias table indicates that there is a high risk that patients selected for pre-emptive transplantation differ from those who were not. For most studies, it was uncertain whether appropriate adjustments were done to correct for this potential imbalance.

First, they are more likely to receive a kidney from a living donor, a condition associated with better outcomes. Then, several studies have pointed out that socio-economic conditions of patients who receive pre-emptive transplantation are significantly better. They display higher education levels [31], are more wealthy [2] and have more frequently private health insurance [32]. US registries also reported ethnical differences

characterized by a higher proportion of Caucasians and non-Hispanics [2, 33] in the pre-emptive group. All these factors are known to be associated with better transplant outcomes that could partly explain the higher graft and patient survival after pre-emptive transplantation.

Furthermore, the patients who are pre-emptively registered on the waiting list have a better health condition. They present fewer cardiovascular comorbidities, have higher haemoglobin and albumin levels and were referred earlier to a nephrologist when compared with the patients placed on the waiting list after having started dialysis [34], which also contributes to improve the results after transplantation.

Even if we hypothesize that the improved patient and graft survival is biased because of confounding factors, we could not see any signals of worse outcomes with pre-emptive living donor kidney transplants. In particular, rates of acute rejections were generally lower with pre-emptive kidney transplantation, and there were no signals of non-adherence that were feared because of no prior experience with dialysis.

Remarkably, only two studies report long-term complications of transplantation, such as occurrence of malignancy (one study) or infection (two studies). It is thus not possible to gauge the impact of pre-emptive transplantation on these important long-term outcomes.

Taking into account that living donation expands the available donor pool, that pre-emptive transplantation seems to have beneficial effects and that eventual negative effects for the donor would not be different between pre-emptive versus non pre-emptive transplantation, the Descartes Working Group judged that at least patients should be informed about the option of pre-emptive living donation during pre-end-stage renal disease counselling.

However, it remains important that during the informing of the donor, sufficient attention is paid to explain potential short- and long-term risks for the donor.

What do the other guidelines state?

We did not retrieve any guideline body providing guidance on this topic.

AT WHAT GLOMERULAR FILTRATION RATE LEVELS COULD PATIENTS BE WAIT-LISTED FOR A PRE-EMPTIVE KIDNEY TRANSPLANTATION?

We recommend that pre-emptive transplantation is organized such that dialysis is avoided in a patient who otherwise would have to start it according to current guidelines (1A).

Why did we ask this question?

Previous guidelines recommended performing a pre-emptive kidney transplantation from a living donor when the glomerular filtration rate (GFR) was below 15 mL/min [35]. However, transplantation is associated with a small increased

risk of death in the early weeks/months after the procedure. Furthermore, the intervention also puts the donor at a small but definite increased risk of complications, including death, after kidney harvesting. Therefore, pre-emptive transplantation must not be performed too early, as it may harm both donor and recipient without reason.

What did we find?

Only a limited number of studies have compared transplant outcomes when pre-emptive transplantation was performed at different levels of GFR. Neither patient nor graft survival was influenced by the level of pre-transplant GFR (>20, 15–20, 10–15 or <10 mL/min/1.73 m²) [36–38].

How did we translate the evidence into the statement?

The optimal timing for pre-emptive Tx should be ‘shortly or a few months before the need to initiate dialysis’. In line with the IDEAL study [39], this is when uraemic clinical symptoms or biochemical abnormalities supervene. This will usually happen when the GFR is between 7 and 10 mL/min [39]. Furthermore, pre-emptive transplantation should be performed only in recipients who have a renal disease that is definitely irreversible and clearly progressive. Beyond GFR, some further information on the speed of kidney function decline can be gained by considering parameters such as urine albumin/creatinine ratio and the levels of serum calcium, phosphorus, bicarbonate and serum albumin. These parameters have been computed into a ‘kidney failure risk equation’ (freely downloadable, <http://www.qxmd.com/Kidney-Failure-Risk-Equation>) that helps to predict when dialysis will be needed with a better accuracy than GFR alone [40]. However, it should be realized that predicting evolution of GFR in the individual patient can be cumbersome.

The timing of the pre-transplantation work-up of both donors and recipients should be done some weeks/months before the planned transplantation, according to centre practices.

The position statement stresses that pre-emptive Tx should be planned in order to avoid dialysis, and is not based on a fixed, pre-determined level of GFR but rather should take into account both clinical and biochemical evidences.

SUGGESTION FOR FUTURE RESEARCH

To set-up a quality registry with the aim to:

- compare the GFR at which patients are pre-emptively transplanted in different countries in Europe.
- measure the outcomes of these patients in terms of patient and graft survival, quality of life and adverse events (infection, cancer, major adverse cardiovascular events) and associate them with estimated glomerular filtration rate (eGFR) at pre-emptive transplantation register outcomes of their living donors in terms of mortality, QoL, major cardiovascular events and evolution of eGFR and albuminuria.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Ferrari. Nurturing the benefits of preemptive kidney transplantation. *Nephrol Dial Transplant* 2016; 31: 681–682)

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METHODS FOR GUIDANCE DEVELOPMENT

Composition of the guidance development group

Descartes and ERBP joined forces to develop this position statement on pre-emptive kidney transplantation. The guidance development group consisted of experts in kidney transplantation, adult and paediatric nephrology, who are all members of the Descartes group. ERBP provided support in guidance development and systematic review methodology. The systematic review that was carried out to inform this position statement complies with ERBP's guidance development methodology standards [41].

Framing of the questions

Two specific clinical questions were developed within the guidance development group:

- (i) Does pre-emptive transplantation with a kidney from a living donor improve outcomes after transplantation?
- (ii) At what GFR levels could patients be wait-listed for a pre-emptive kidney transplantation?

The clinical questions were translated into the PICOM format with pre-specification of the eligible target **P**opulation, **I**ntervention, **C**omparator, **O**utcome and study design **M**ethodology, and explicit inclusion criteria for study selection were defined (Appendix 1).

Literature search and study selection process

A search strategy with Boolean combinations of terms for 'kidney transplantation' and 'pre-emptive' was constructed (Appendix 2) and used to identify eligible studies in MEDLINE and EMBASE. Both databases were searched on 16 May 2013,

results of both databases were combined and de-duplicated (Supplementary data, Appendix 3). Two guideline development group members performed screening by title and abstract independent from each other and assessed the full text of each potentially relevant study to determine eligibility for inclusion using the pre-defined inclusion criteria defined within the PICOM framework. Discrepancies were resolved by discussion within the group.

We included all study designs in humans with the minimum requirement of at least one patient in both treatment groups without any language restrictions that compared pre-emptive kidney transplantation with transplantation after dialysis treatment had been initiated. We excluded case reports, narrative review articles and editorials without primary data.

Data extraction and risk of bias assessment

Relevant information on design, conduct, characteristics of study participants, outcomes and risk of bias were collected from each included study in duplicate by two guideline development group members independently from each other using a standardized form. Risk of bias of the included studies was assessed using validated checklists, the Cochrane Risk of Bias tool for randomized controlled trials [42] and the Newcastle Ottawa scale for Cohort and Case-control studies [43]. Results of the data extraction of each individual study were then used to generate summary of findings tables per outcome across studies and for the risk of bias of each domain per study (Supplementary data, Appendix 3).

Formulating and grading recommendations

The guideline development group used the data extraction tables and summary of findings tables to formulate and grade the recommendations. We applied the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) methodology to grade the quality of the evidence and the strength of the recommendations [44].

Writing the rationale

Guideline development group members wrote the rationale according to a pre-specified format that outlines relevant background information on the topic, reviews the evidence and states how the evidence was translated into the statement.

APPENDIX 1

Clinical question structured in PICOM format.

Is preemptive kidney transplantation from a living donor compared to kidney transplantation from a living donor after initiation of dialysis treatment associated with improved outcomes?

Population	Adult and pediatric recipients of a kidney transplant from a living donor
Intervention	Preemptive kidney transplantation from a living donor
Comparator	Kidney transplant from a living donor after initiation of dialysis treatment

Outcomes Patient survival, graft survival, acute rejection, infection, malignancy

Methods Randomized controlled trials, cohort studies, case-control studies, minimum requirement is $n = 1$ in each group (intervention and comparator group)

- (1) exp Kidney Transplantation/
- (2) pre-emptive.tw.
- (3) preemptive.tw.
- (4) pre?mpti\$.tw.
- (5) or/2-4
- (6) 1 and 5

APPENDIX 2

Search strategy for MEDLINE and EMBASE

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