Guidelines on Renal Transplantation

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European
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of Urology

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1. INTRODUCTION

Most renal transplantation centres in Europe were founded by urologists. However, many of them are becoming part of transplant centres run by general transplant surgeons. This is a main reason why it is important to present current knowledge about renal transplantation in these European Association of Urology (EAU) guidelines.

As renal transplantation is very much an interdisciplinary field, the Guidelines Group contains not only urologists but also an immunologist (Prof. Dr. Süsal) and a nephrologist (Prof. Dr. Budde). Besides medical and technical aspects, the Guidelines Group has also considered ethical, social and political aspects. This was necessary because of the still-increasing gap between 'supply' and 'demand' for kidney transplants, and the large differences in organ donation rates between several European countries, suggesting European countries can learn from each other on how to increase organ donation rates.

There are few prospective randomised studies for most sections of the Guidelines, and sometimes none. Thus, the grades of recommendation, which are evidence-based, seldom exceed grade C. Instead, the Guidelines are well supported by a wealth of clinical experience based on several decades of work in renal transplantation, as in, for example, technical aspects of transplantation and explantation.

A level of evidence (LE) and/or grade of recommendation (GR) have been assigned where possible (1).
The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Publication history information:
The Renal Transplantation Guidelines were first published in 2003, with a partial update in 2004 followed by this full text update in 2009. Additionally, a quick reference guide is available. All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/professional-resources/guidelines/.

Levels of evidence and grade of guideline recommendations*

Table 1: Level of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 2: Grade of recommendation

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**modified from Sackett et al. (1)*

1.1 REFERENCE

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
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2. KIDNEY DONATION

2.1 Ethical issues in transplantation

2.1.1 Primary ethical principles

A number of primary principles are widely accepted as forming the bedrock of medical ethics (1-4). Conflict in an individual case often arises in trying to adhere to all these principles at the same time.

2.1.1.1 Beneficence: doing good, avoiding harm, autonomy, fairness

A central tenet of medical ethics is the obligation to strive at all times to do good for the patient. Although no physical good will accrue to a donor, it is generally accepted that the psychosocial benefits to the living donor justify the risks involved (5).

Making sure there is an appropriate balance between benefit and harm is an important clinical judgement. A high standard of donor assessment and risk limitation is therefore of paramount importance before living kidney donation can take place (6).

Individuals are said to have 'decision-making capacity' if they able to understand relevant information, consider its implications, and come to a communicable decision. A donor's decision to donate should be respected.

The principle of justice is very important in kidney distribution, where demand far outstrips supply, which means there is a ranking system for allocating organs in an order of priority that can be morally justified. In transplantation, scarce resources usually have to be carefully allocated to recipients chosen from a larger pool of the population.

2.1.2 Deceased donor organ donation

There has been an increase in living-donor organ procurement in recent years. Most organs still come from deceased donors, brain-dead donors, and organs from the non-heart beating donor (NHBD) procurement programme, now used by several transplant centres. However, this resource base is shrinking. Together with an ever-increasing rise in potential recipients, this causes considerable pressure on the transplantation programme.

2.1.2.1 Deceased organ donor

In most countries, obtaining consent to proceed with organ donation is a major challenge.
The process of gaining formal consent from relatives or from the patient during life can be defined as 'opting in' to a donor scheme. Unless consent is expressly given, the presumption is that consent is withheld.

In some European countries, the opposite situation applies. Consent is presumed unless the patient has specifically opted out before death. This type of legislation can increase organ donation. For example, in Spain, this approach has produced a national network of medical teams dedicated to obtaining the maximum number of donors and greatly increasing organ transplantation (7).

2.1.2.2 Allocation of deceased donor organs

Who 'owns' deceased donor organs and who makes the decision regarding allocation are both issues in need of clarification (8-10). However, there is a general presumption that the State holds the responsibility for allocation or disposal of donated organs, which is then delegated to the appropriate transplant team (11). It is considered unacceptable that deceased donor donation and allocation should depend upon the personal attributes of the recipient, e.g. race, religion or wealth. In kidney transplantation, the European healthcare systems attempt to maximise benefits by distributing kidneys on the basis of (HLA) matching. Potential recipients are allocated points for waiting time, matchability and sensitisation. Kidney distribution systems should be transparent and regularly audited.

2.1.3 Living-organ donors

The ethical approach to organ donation is guided mainly by those rules that seek to be charitable. Living-donor transplant has been regarded as a regrettable necessity because of the success of living-donor transplant (as judged by graft and patient survival) and the scarcity of deceased donor organs (12). The chronic shortage of deceased donor organs has led to a more general acceptance of living-donor transplants. The physical and psychosocial well-being of the donor are of primary importance. Each donor should have an advocate (i.e. a psychiatrist and nephrologist from the donor evaluation team) to provide unbiased advice on the donation process and there should be separation of the recipient and donor teams.

Kidneys can be accepted from related and unrelated donors, including spouses, friends, and acquaintances or altruistic donors (anonymous donors) or paired kidney donation (see Section 2.3.3.1).

The donor must be given a psychosocial evaluation by a mental health professional, who has no relationship with the recipient, to assess the donor's ability to make his or her decision. The donor's confidentiality must be protected and the evaluation must be carried out in the absence of the recipient. If a translator is necessary, the translator must be unknown to both the recipient and donor. The donor should be told about the benefits to the recipient's health (physical and mental) and the risks to the donor's health (physical and mental).

The donor's motivation should be assessed. Coercion and secondary gain (monetary or other personal gain) should be excluded. Outcomes should be discussed, psychological benefits after a successful transplantation (increased self-esteem) and resentment or depression after an unsuccessful transplantation.

Recommendations
• It is the right of individuals to donate as well as to receive an organ
• Commercially motivated renal transplantation is unacceptable. It has been widely prohibited by law and is strongly opposed by the International Society of Transplantation
• With the increasing success of living-donor transplants, as judged by graft and patient survival, and with the scarcity of deceased donor organs, living-donor transplants should be encouraged. The appeal of using living donors in renal transplantation is partly due to the ongoing shortage of deceased donors
• The altruistic living donor must give informed consent, which can only be obtained if he or she has a proper understanding of the risk involved
• A patient should be treated as an 'end', and not as a 'means'. Respect for dignity, integrity and authenticity of the person are basic human rights
• Living unrelated donors should only be accepted after the local ethical committee has given permission according to the rules of the country in which the donation is taking place

Because ethical values cannot be measured using the 'scientific' basis of levels of evidence, grades of recommendation are not given

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2.2 Policies to increase the supply and use of deceased donors

Generally, the gap between supply and demand of kidneys has tended to stabilise in countries with a donation rate greater than 40 kidneys per million population (pmp), but has increased in countries with a lower donation rate. This is in spite of the trend for donation rates to increase (or stabilise) in Europe since 2001. Table 3 lists recent kidney transplant rates in different European countries (1).

Table 3: Kidney transplant rates in 2007 (1)

Country	Deceased donor kidneys (pmp)	Living-donor kidney (pmp)	Total kidneys (pmp)
Austria (ET)*	37.2	7.5	44.7
Belgium (ET)*	40.3	4	44.3
Bulgaria	1.5	2.2	3.7
Croatia (ET)*	13.8	4.5	18.3
Cyprus	25.7	51.4	77.1
Czech Republic	35.2	3.3	38.5
Denmark (ST)**	21	10.2	31.2
Estonia	38.6	3.7	42.3
Finland (ST)**	31.8	1	32.8
France	42.3	3.7	46
Georgia	0	1.8	1.8
Germany (ET)*	27	6.9	33.9
Greece	9.2	7.9	17.1
Hungary	26.2	1.7	27.9
Iceland (ST)**	0	22.4	22.4
Ireland	31.9	1.2	33.1
Italy	26.1	1.7	27.8
Latvia	31.3	0.4	31.7
Lithuania	24.4	2.7	27.1
Luxembourg (ET)*	25	–	25
Malta	12.5	5	17.5
Moldova	0	0.6	0.6
Netherlands (ET)*	26.6	21.8	48.4
Norway (ST)**	36.8	18.2	55
Poland	17	0.6	17.6
Portugal	40.8	3.5	44.38
Romania	3.33	7.23	10.56
Slovak Republic	36.8	2.6	39.4
Slovenia (ET)*	14.9	–	14.9
Spain	45.9	3	48.9
Sweden (ST)**	27.9	13.4	41.3
Switzerland	21.6	13.2	34.8
Ukraine	1.2	1.6	2.8
United Kingdom	20.1	13.4	33.5

pmp = per million population.

* ET = Country member of the Eurotransplant.

** ST = Country member of the Scandia Transplant.

The data suggest that a donation rate of 40 pmp per year should be achievable by any single country in Europe, especially with so many sociocultural similarities. However, the act of donation is complex, depending on many factors and interactions, few of which have been proven useful individually or are generally applicable throughout the European Union. Although it is relatively easy to set a minimum standard for organ donation, it is more difficult to recommend specific, donor-promoting activities for individual countries and professional organisations. However, a few options are described below.

2.2.1 Donor cards

Some countries such as the UK require donors to ‘opt in’. Others, such as Belgium and Denmark, ‘presume consent‘ and allow individuals who do not want to be donors to ‘opt out’.

Many countries have publicity schemes encouraging the general population to carry donor cards or register their wish to donate (opting-in) on a computerised donor register. This helps to reduce the risk of donation being refused by the family. In the UK, 15.1 million individuals are registered on the 'opting-in' computer, while 5-10% of the population prefer to carry donor cards (2). However, the efficiency of this 'opt-in' system in creating donors is lower than in countries with a presumed consent. Opt-in systems require continuous publicity to increase the number of opted-in donors and transplant centres. Intensive care physicians and transplant co-ordinators also need to access the register routinely to identify potential deceased donors.

Recommendation	**GR**
• In all countries without presumed consent law, efforts should be increased to recruit donors through an opting-in register or by carrying donor cards	C

GR = grade of recommendation

2.2.2 Improved organisation and resources

Services must be better organised and resourced to increase deceased donor donation. The ability to achieve more than 25 donors pmp increases with the number of intensive care beds. High-donating countries with better-resourced intensive care units (e.g. Spain, France, Belgium) have increased the number of staff responsible for donation (transplant co-ordinators) and given them proper financial support. Successful education programmes, such as European Donor Hospital Education Programme (EDHEP) (3) or institutional audits, such as Donor Action, have increased and maintained the awareness of intensive care physicians for the need for deceased donor donation and supported them in approaching donor families to discuss donation. Transplant co-ordinators are responsible for liaising with coroners and public relations, particularly avoiding adverse publicity.

Recommendation	**GR**
• Professional organisations within countries should, where necessary, put pressure on government health departments to maintain enough intensive care beds, create a cadre of national transplant co-ordinators, and fund and deploy educational programmes for intensive care physicians	C

GR = grade of recommendation

2.2.3 'Opting-out' legislation

The introduction of opting-out legislation results in increased rates of deceased donor donation. All European countries with more than 30 kidney donors pmp per annum (see Table 3) have opting-out legislation. Adverse publicity results in a 'soft' presumed consent in most countries, which also takes the family's views into account. Countries with informed consent do not usually perform as well, with the USA producing the highest kidney donation rate of 24 donors pmp through the United Network for Organ Sharing/The Organ Procurement and Transplantation Network (UNOS/OPT) (4, 5).

Recommendations
• A recommendation cannot be made about something as fundamental as changing the law on deceased donor donation
• However, presumed consent with an opting-out law is desirable

2.2.4 Non-heart-beating donor (NHBD)

Non-heart-beating donors provide an important opportunity to decrease the deceased donor shortage of kidneys, even though NHBD kidneys are suboptimal organs due to the increased risk of delayed graft function and primary non-function. However, the long-term viability of NHBD kidneys in strictly selected donors has been improved by the use of a continuous perfusion machine on the cadaver before harvesting (6).

A continuous perfusion machine can be used to assess NBHD kidney viability. Flow measurements and urinary enzyme excretion (7) are predictors of viability. Presumed consent legislation would allow many more NHBD kidneys because rapid intra-arterial cold perfusion of a recently deceased person would normally be allowed before family members arrive at the hospital. However, under informed consent law, perfusion of a cadaver without relatives' permission is an unwarranted assault. In contrast, under presumed consent, a coroner is able to give permission for perfusion without requiring the relatives' consent, so allowing the use of NHBD to be expanded significantly.

Recommendations	GR
• Greater use of NHBDs should be made	B
• Transplant staff should create policies for recently dead admissions to casualty departments to be used as NHBDs	B
• Local coroners should be consulted regarding the legal implications	B

GR = grade of recommendation.

2.2.5 Elderly donors

The use of kidneys from elderly donors (> 60 years) is increasing. In countries such as Spain, it represents 40% of total kidney transplants. Long-term survival of kidneys is similar to the transplants performed with non-expanded criteria donors (8). After 6 months' post transplant, patients who have been transplanted have a better survival rate than patients remaining on dialysis. Kidney transplants from donors older than 70 years carry a higher risk of graft loss and mortality, especially when transplanted to recipients under 60 years (9).

Recommendations	GR
• The use of carefully selected donors over 60 years should be maintained and encouraged as a continuing source of deceased donor kidneys	B
• Donors over 70 should be evaluated on an individual basis, taking into account that better results are obtained when transplanted to patients older than 60 years	B

GR = grade of recommendation.

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2.3 Policies to enhance living donation

Kidney transplants from living donors offer a better graft and patient survival than those from deceased donors (1). Two major recent developments have led to the increased acceptance of living kidney donation:

- Kidney transplant results have improved so that more patients with end stage renal disease (ESRD) have opted for transplant rather than dialysis
- As the number of deceased donor kidneys has not increased, the number of living donors has increased.

It is also likely that laparoscopic donor nephrectomy (less time off work, shorter hospital stay) has helped recruit living donors.

The USA have greatly improved the supply of kidney transplants by recruiting more than 50% of total donations from consanguineous and non-consanguineous donors (i.e. living unrelated donors, which make up 40% transplants from living donors) (2, 3). In contrast, in Europe, living-donor transplants make up only 15% of transplantations. However, there is a clear trend for an increase in the living-donor rate, especially in the Scandinavian countries, The Netherlands and Cyprus (see Table 3). Living-donor rates can be improved at different stages in the referral process and in more general ways (Table 4).

Table 4: Ways of improving the living donation rate

During referral process	
•	Nephrologists, at non-transplanting as well as transplanting centres, should be encouraged to discuss openly living donation with families of patients suffering ESRD, preferably before the patient begins dialysis. This results in pre-dialysis transplantation, increased transplant rates and better use of dialysis resources
•	Counselling (e.g. by senior nurse practitioners or living-donor co-ordinators) should be available to discuss screening tests, provide information packs, and arrange reimbursement of necessary donor expenses allowed in law
•	If legally permitted, living unrelated donors should be encouraged
More general methods	
•	Medical methods, such as laparoscopic harvesting, paired kidney exchange, transplantation of grafts with anatomical abnormalities (vascular, urinary tract fusion), reversal of a positive cross-match by treatment with plasmapheresis, and intravenous immunoglobulin administration
•	Ethical methods, such as showing appreciation for organ donation
•	Organisational methods, such as medical leave for organ donation and reimbursement of all costs to the donor

Recommendations		**GR**
•	Living donation in Europe should be encouraged. There is a widening gap between donation and demand for kidney transplants, with not enough deceased donors. There is, however, an increase in living donors. In the USA, the number of kidneys from living donors is nearly the number of kidneys from deceased donors.	C
•	Organ donation should be considered a charitable gift. Society can express gratitude to organ donors for their gift as with charitable contributions, without jeopardising its altruistic basis (e.g. 'Medal of Honor', limited reimbursement, medical leave, priority access to organ for transplant, donor insurance).	C
•	All nephrologists who care for ESRD patients should explore the living donor option with the family when a patient first presents with ESRD	

ESRD = end stage renal disease; GR = grade of recommendation

2.3.1 Medical methods to increase number of living donations

2.3.1.1 Acceptance of grafts with anatomical anomalies

The use of grafts with anatomical anomalies is considered a relative contraindication by most experienced transplantation centres because of the shortage of living donors. Anatomical anomalies include renal cysts, uretero-pelvic junction obstruction, solitary stones > 1 cm, duplex ureteral system and multiple arteries and veins. However, retrospective reports have suggested that grafts with multiple renal artery or vein anomalies, such as circumaortic or retroaortic renal vein, do not carry an increased risk of complications in experienced hands (4).

If the donor has a good immunological correspondence with the recipient, but an abnormal kidney, which is the only kidney available, and if the recipient on haemodialysis has a poor status, the abnormal kidney should be transplanted leaving the donor with the best one.

A laparoscopic right kidney donor nephrectomy is as safe as a left nephrectomy. A recent prospective trial showed no differences in complication rates and graft survival between left- and right-sided donor nephrectomy (5).

Recommendations		**GR**
•	Multiple renal artery or grafts with anatomical anomalies are not absolute contraindications. Decisions should be made on an individual basis	C

•	Laparoscopic right kidney nephrectomy is as safe as left nephrectomy in terms of complications and graft survival	A

GR = grade of recommendation

2.3.1.2 Laparoscopic living-donor nephrectomy (LLDN)

Laparoscopic living-donor nephrectomy (LLDN) is an alternative surgical method that has increased the rate of living donations. It is becoming the preferred technique for living-donor renal transplantation. In the USA, laparoscopic donor nephrectomies are more common than open surgery donor nephrectomies. In Europe, although increasing, fewer laparoscopic nephrectomies are performed than open procedures (6).

There is a good evidence base for LLDN, including three systematic reviews, which have compared its safety and efficacy to the 'gold standard' of open donor nephrectomy, at least seven randomised control trials (level of evidence: 1-2), five prospective non-randomised studies (level of evidence: 2), and several retrospective studies (7-9). Compared to open live donor nephrectomy (OLDN), LLDN shows similar rates for graft function, rejection rate, urological complications, and patient and graft survival. However, measures for analgesic requirements, pain, hospital stay, and time to return to work are significantly better for a laparoscopic procedure.

In terms of donor safety, the historical mortality rate is 0.03% with open donor nephrectomy, a rate unchanged by the introduction of LLDN (10, 11). The data about potential mortality should be included in all informed consent. In addition, LLDN does not affect the long-term risk of developing ESRD (12). However, the laparoscopic approach takes longer and requires additional resources. Nevertheless, the shorter hospital stay and more rapid return to work may compensate for the initial higher costs. In addition, the number of live kidney donations has increased by more than 100% in many institutions since the introduction of the laparoscopic approach.

Overall, laparoscopic nephrectomy offers donors less post-operative pain, shorter convalescence, and better cosmetic results, compared to traditional open donation. In experienced hands, this procedure is accomplished without increased risk to the donor's safety or allograft function. As with OLDN, LLDN should be considered the gold standard of treatment.

Table 5: Laparoscopic live donor nephrectomy: advantages and disadvantages

Advantages	**Disadvantages**
• Less post-operative pain	• Graft loss or damage during 'learning curve'
• Minimal surgical scarring	• Pneumoperitoneum may compromise renal blood flow
• Rapid return to full activities and work (about 4 weeks)	• Longer operative time
• Shorter hospital stay	
• Magnified view of renal vessels	

Recommendations	**GR**
• Laparoscopic nephrectomy offers equal urological complications, graft function and graft survival than open nephrectomy, with less post-operative morbidity, shorter convalescence and better cosmetic results	A
• Laparoscopic nephrectomy increases the number of individuals willing to donate. It should be used only by appropriately trained and experienced surgeons.	C

GR = grade of recommendation

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2.3.1.4 ABO-incompatible donors

ABO incompatibility was once a contraindication for renal transplantation, but this is no longer the case because of new techniques (antibody adsorption columns) (1) and new immunosuppressive tools (e.g. anti-CD20 monoclonal antibody, rituximab) (2). This has increased the opportunities for organ donation. Successful transplantation case studies have been reported in living donors against a blood group barrier, with retrospective studies showing similar outcomes to those of blood-group-compatible transplants (3, 4). Limitations of the current reports are the small patient numbers, relatively short follow-up periods and differences in treatment protocols (5, 6). Further investigation is ongoing (7-10). Current reports indicate that ABO-incompatible transplantation require a more intense and more costly immunosuppressive therapy (11-13) (level of evidence: 3).

Until more long-term data are available, and key issues of the treatment protocol are solved, this procedure remains experimental and should only be performed as part of a scientific trial. Patients should be counselled on the potential risks (more intense immunosuppression, lack of long-term outcome data) and benefits (immediate availability of a living donor). Other transplantation methods should be considered, such as cross-over transplantation, which allows timely transplantation using standard immunosuppressive protocols (level of evidence: 3).

Recommendations	GR
• ABO-incompatible transplantation is a promising procedure undergoing clinical evaluation	C
• Due to its experimental nature, it should be performed in experienced centres under scientific documentation	C
• Patients should be counselled about potential risks and alternatives	C

GR = grade of recommendation

2.3.1.5 Cross-match-positive living-donor kidney transplants

This was previously thought to be a contraindication. However, several pilot studies (11-14) have reported successful transplantation with acceptable short-term results, using extensive antibody elimination strategies

(e.g. plasmapheresis), intravenous application of immunoglobulins, and a more intense immunosuppression with antibody induction and the use of B-cell depleting agents (e.g. anti-CD20 antibody rituximab). (Level of evidence: 3)
Due to lack of standardized treatment protocols and paucity of long-term results of larger cohorts this procedure remains experimental and should only be performed as part of a scientific trial. Patients should be counselled adequately on the potential risks. Alternative ways for transplanting highly immunised patients (e.g. Eurotransplant Acceptable Missmatch programme , cross-over transplantation) should be considered to allow a timely transplantation of these patients with standard immunosuppressive protocols (15, level of evidence: 4).

Recommendation	**GR**
• Transplantation of cross-match positive living donors is an experimental procedure, which should only be performed in scientific trials. Patients should be counselled about risks and potential alternatives.	C

GR = grade of recommendation

2.3.1.6 Living unrelated kidney donation
In many countries in Europe, altruistic non-consanguineous kidney donation is allowed legally, provided checks are made for altruistic motivation and financial gain excluded (15, 16). The results are comparable to related living donation (level of evidence: 3).

Recommendation	**GR**
• Living related and unrelated donation should be encouraged within national laws	B

GR = grade of recommendation

2.3.1.7 'Non-directed' living-donor transplantation
'Non-directed' living-donor transplantation between an altruistic donor and a recipient unknown to the donor is being performed in a few centres worldwide (17-19). Though controversial, there seem no moral or social reasons to exclude such truly altruistic donors (16, 20). However, there are ethical and legal concerns about this type of donation (21), which at the moment make it difficult to recommend in these guidelines.

2.3.1.8 Payment to living donors from a central organisation
Although paying living donors to donate organs from a central organisation would be a potential way of increasing organ availability in an era of organ shortage (22), it is generally agreed that the payment of living donors to donate organs is ethically unjustifiable (23, 24). It is strongly recommended that all organ donors have adequate lifelong access to medical care for the prevention of renal failure and potential side-effects of organ donation (15, 16).

The cornerstone of clinical transplantation has been the altruistic donation of kidneys from living relatives. The gift of a transplant is priceless and societies that support transplantation have generally refused to give a monetary value to a transplantable organ or tissue. In Europe, it is illegal to make a payment for living related organs and The World Health Organization (WHO) has stated that the body and its parts cannot be the subject of commercial transactions, and all giving and receiving of payments should be prohibited (24) (level of evidence: 4).

Recommendations	**GR**
• Legislation in every European country forbids payment for organs	C
• Donation of an organ should remain a gift of live without any financial impetus	C

GR = grade of recommendation

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2.3.2 Ethical ways of showing appreciation for organ donation

2.3.2.1 Donor 'medal of honour'

Organ procurement organisations could have ceremonies which recognise and honour organ donation. A donor 'medal of honour', given by a top official of a country, would effectively express appreciation and gratitude on behalf of the whole community to the living donors and families of deceased donors (1, 2).

Policymakers, ethicists and the transplant community cannot agree on whether giving benefits to the families of organ donors would increase organ availability (3) (level of evidence 4). Because of the lack of evidence, no general recommendation can be made on whether or not to provide incentives for living donors or families of deceased donors.

2.3.3 Organisational ways to encourage organ donation

2.3.3.1 Cross-over transplantation or paired organ exchange

A cross-over renal transplantation or a paired kidney exchange transplant is an exchange between two or more couples, who are prevented by ABO incompatibility or positive cross-match from donating their kidneys to their preferred recipients. The problem may be solved by exchanging the living donor kidneys between pairs of couples to achieve a cross-match negative or ABO-compatible combination.

The inclusion criteria should favour the exchange of equivalent kidneys in size and age. A programme of cross-over kidney transplantation allows an exchange of organs between two living donors (4), or in some countries, from one living donor and one deceased donor (5). By using paired kidney exchange, the recipients are able to benefit from living donation. Paired kidney exchange also reduces the duration of dialysis before transplantation and expands the pool of living donors (6). Graft survival rates of paired kidney exchange are similar to directed, compatible live donor transplants (7) (level of evidence: 3).

Recommendation	**GR**
• Paired kidney exchange if permitted by national law is a way of increasing the number of kidney transplants	C

GR = grade of recommendation

2.3.3.2 Medical leave for organ donation

No-one should have to incur a personal expense for donating an organ (8). Many countries legally provide 30-days' paid medical leave to all employees who donate an organ for transplantation (9). The American Society of Transplantation has recommended living donors should be given leave from employment similar to parental leave granted for a new baby (level of evidence: 3).

Recommendations	**GR**
• The health and well-being of living donors should be monitored in a follow-up register to document any long-term medical problems due to donation B	B
• There should be a national insurance plan that provides life and disability insurance for all living donors	B

GR = grade of recommendation

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2.4 Kidney donor selection and refusal criteria

2.4.1 Introduction

A diagnosis of brain death is required in a comatose subject who may potentially be a deceased organ donor. The potential donor must be evaluated for any transmissible pathological condition and the quality of any organ(s) being considered for transplantation.

The short-term results of transplants with kidneys from donors over 65 years old are almost similar to those with younger organs. However, long-term graft survival is lower (1). In addition, the main physiological risk factor in 'older' kidneys is a prolonged cold ischaemia time (2, 3). In keeping with these observations, the modern definition of a suitable donor places less emphasis on age and more on the physical condition of the donor, especially of the organ to be donated. The aim is to reduce the possibility of discarding usable organs. Thus, there are now no absolute age limits to donation. However, a short ischaemia time is mandatory, as well as careful donor selection, particularly because older donors have more co-morbidity. There is a similar trend towards extending the upper age donation limit in living donors to over 55 years (4).

2.4.2 Infections

The potential donor must be checked for infectious diseases (Table 6):

Table 6: Infections to be checked for in potential donor

•	Human immunodeficiency virus-1, -2 (HIV-1, HIV-2)
•	Hepatis C
•	Hepatitis B surface antigen (HBsAg), anti-HBc; acute hepatitis (liver enzymes)
•	Cytomegalovirus (CMV)
•	Epstein-Barr virus (EBV), only in paediatric recipients
•	Active syphilis
•	Viral infection, sepsis, tuberculosis, infections of unknown aetiology
•	Family history of (or clinical signs that may be caused by) Creutzfeldt-Jacob disease

There is a high risk of HIV transmission from potential donors with suspected intravenous drug abuse. In addition, serology tests during the incubation period of HIV (2 months) or hepatitis (up to 6 months) may be

negative, while large amounts of fluids administered during a resuscitation attempt can result in a normal serology due to dilution effects (5). Serological tests must therefore be repeated and additional tests done (e.g. polymerase chain reaction) to rule out infection.

2.4.3 Special exceptions for infections

Different circumstances apply when an organ recipient is already infected with HIV or hepatitis (Table 7).

Table 7: Exceptions for organ recipients who already have infections

HCV-positive donor
• In an HCV-positive recipient, transplant is allowed following informed consent
• In an HCV¬-negative recipient, there is a high risk of disease transmission. However, transplant may be possible in emergency situations following informed consent
HBsAg-positive donor
• In an HBsAg-positive recipient (if HDV antigen is negative), transplant is allowed after informed consent
• In an HBsAg-negative recipient with high anti-HBs antibody titre and HBc positivity, transplant is allowed after informed consent
• In an HBsAg-negative recipient with intermediate/high anti-HBs antibody titre alone (Hbc-antibody negative), transplantation may carry a higher risk but is allowed after informed consent
• In an HBsAg-negative recipient with undetectable anti-Hbs antibody, transplant is allowed only in a life-saving situation, when HDV antigen is negative and following informed consent
HBc-antibody-positive donor
• In liver transplantation, there is a high risk (50%) of transmitting hepatitis B from an anti-HBc antibody-positive donor to the recipient. In this situation, liver transplantation is allowed after informed consent. Kidneys, heart and lungs carry a low, but not absent, risk of hepatitis B transmission, so kidney transplant is allowed in an HBsAg-positive recipient, or an HBsAg-negative recipient with anti-HBs antibody titre ≥10 mIU/mL, following informed consent
• In an HBsAg-negative recipient with no anti-HBsAg antibody, only life-saving transplants are allowed, after informed consent

2.4.4 Malignant tumours

A previous history of malignancy is not usually a contraindication for organ donation. However, there are some absolute contraindications that make a donor unsuitable for transplant. These are active cancer or a history of metastatic cancer (with a few exceptions, such as testicular cancer) and cancers with high recurrence rates, such as advanced breast carcinoma, melanoma, leukaemia, or lymphoma. In addition, when a potential donor has experienced a brain haemorrhage of unknown aetiology, metastasis must be excluded as a cause of intracranial bleeding. For example, the serum level of human chorionic gonadotropin must be measured to exclude chorioncarcinoma in female donors.

With other cancers, if less than 10 years has elapsed since completion of treatment, a careful risk-benefit assessment must be done of the risk of disease transmission versus mortality on the waiting list. The donor shortage has led to many transplant programmes accepting donors after only 5 years' absence of recurrent malignancy. So far, only a low incidence of donor-transmitted malignancies has been observed (6). Successful renal transplants have been performed with kidneys affected by small, low-grade renal carcinomas that were completely excised. Recipients of organs from donors with a history of malignancy must be informed and carefully monitored (7).

2.4.5 Special exceptions for malignant tumours

For special exceptions in malignant tumours, see Section 8.1.

2.4.6 Vascular conditions and renal function

Important risk factors for organ failure are a prolonged history of diabetes mellitus or serious hypertension with retinal vascular damage. Factors for excluding potential donors or for considering a donor as a single- rather than a multi-organ donor include:

- Previous myocardial infarction
- Coronary bypass and angina
- Severe systemic vascular disease
- Events of long-lasting hypotension
- Oliguria
- Long-lasting intensive care stay.

A donor's renal function should be evaluated at admission using creatinine clearance (Cockcroft-Gault formula), which corrects the serum creatinine value for age, body weight and sex (8). The urinary tract can also be assessed by 24-h proteinuria and ultrasound kidney imaging, particularly in elderly donors. In many transplant centres, a calculated creatinine clearance level of 50 mL/min is at the lower range for kidneys usable for two recipients, independent of the histology of the organ, but according to the history of the donor, while other centres evaluate glomerular sclerosis and arteriolar sclerosis from renal biopsy (9).

Acute renal failure is not itself a contraindication. The kidneys may be used after careful assessment (level of evidence: 3).

2.4.7 Marginal donors

The following criteria need to be considered in a marginal organ (10) (level of evidence: 3):

- Age over 70 years without other risk factors.
- Age between 60 and 70 years, with a history of diabetes mellitus, hypertension, clinical proteinuria up to 1 g/24 h, or retinal vascular changes.
- Calculated creatinine clearance of 50 mL/min – the organs are still valuable for a single graft.
- Calculated creatinine clearance < 50 mL/min – the organs should be used as dual graft or discarded if histologically abnormal.
- Approximately 5-20% of glomerulosclerosis at biopsy with at least 25 glomeruli taken from both kidneys – the organs are still valuable for a single or double graft.
- More than 20% glomerulosclerosis – an individual decision has to be made based on renal function.

The true clinical meaning of each criterion is unknown because none of them have been rigorously validated and opinions differ over their individual value, as for example with pre-transplant renal biopsy (11, 12).

2.4.8 One graft or two grafts per recipient

The rationale for dual marginal kidney transplantation is based on two conflicting concepts. Firstly, kidneys with a small nephron mass undergo hyperfiltration and glomerular hypertension, which causes progressive glomerulosclerosis (13). A single marginal kidney has a reduced renal mass and a suboptimal number of nephrons, which are further reduced by cold ischaemia time, transplant trauma and the potential nephrotoxicity of immunosuppressive therapy. Simultaneous transplantation of both kidneys to the same recipient may increase nephron mass and prevent kidney damage.

Secondly, marginal kidneys have a functional reserve only verifiable after transplantation. In addition, the glomerular filtration rate of a transplanted kidney often increases post transplant (14-16). Dual transplantation is redundant because it shortens the organ pool.

These two opposing concepts would seem to suggest that kidneys judged unsuitable based on function or histology should either both be transplanted into a single recipient or both be discarded (17). However, a prospective multicentre study (18) concluded that double-kidney transplants are safe, well tolerated, and result in no more surgical complications than single-graft operations.

To date, the surgical technique for dual renal grafting has not been standardised (19, 20) (level of evidence: 3).

Recommendations	**GR**
• Any brain death comatose subject should be considered a potential organ donor, without age limits	C
• Consensus for organ harvesting should be obtained from relatives or significant others according to local law and policies. Authorisation for explantation by the donor's close relatives is always recommended, even if local legislation on organ donation presumes consent: - Contact between relatives and a well-trained, sensitive professional is very important in establishing favourable public opinion on organ donation - Individuals who objected to donation during life must always be excluded	
• Any donor organ affected by a potentially transmittable pathology (infections, neoplasias) must be carefully evaluated considering the risk-benefit ratio for the recipient B	B
• A good-quality organ must be guaranteed to the recipient and every transplant centre must establish its own guidelines on organ acceptability. Organs from marginal donors can only be used after thorough assessment. The recipients need to be informed and must confirm their acceptance	C

GR = grade of recommendation

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2.5 Explantation technique

2.5.1 Technique of deceased donor organ recovery

Each solid organ should be procured as quickly as possible to minimise ischaemic injury. Removal of the heart, lungs, liver and pancreas (Table 8) usually takes place before kidney retrieval (Table 7) (1-10) (level of evidence: 3). Continuous machine perfusion reduces injuries due to ischaemia or reperfusion and improves the immediate post-operative graft outcome (8-10) (level of evidence: 3).

Table 8: Important considerations during removal of heart, lungs, liver and pancreas

• Infuse 3L of UW (University of Wisconsin) solution into the aorta before organ recovery.
• Open Gerota's fascia to expose the kidneys for surface cooling. While the heart is being removed and the cold perfusate is being infused, place ice slush into the abdominal cavity to provide surface cooling for the liver, kidneys and pancreas
After the heart is removed and the liver is to be retrieved, careful attention should be given to ensure the following:
• Do not extend the aortic cannula beyond the ostia of the renal arteries. This will avoid the risk of inadequate flushing of the kidneys, leading to unnecessary and harmful warm ischaemia
• If the superior mesenteric artery is not being taken along the coeliac artery for the liver, the upper portion of the remaining aorta can be reclamped to allow continued perfusion of the kidneys and cooling during removal of the liver
• If the superior mesenteric artery is taken with the liver and removed, it may not be possible to place a curved forceps in a tangential manner on the remaining segment of aorta. Although this would allow continued flushing of the kidneys, there is a risk of occluding the renal artery orifices, especially on the right side
• During transection of the vena cava between the liver and the kidneys, take care to avoid injury to the right renal vein. The right renal vein can often extend superiorly before entering the vena cava and may be accidentally transected. Because a segment of infrahepatic vena cava is needed in liver transplantation, the kidney retrieval team must be instructed to leave an optimal amount of venal caval cuff to go with the liver to prevent injury to the right renal vein
• The pancreas, if being retrieved, should be removed before the kidney. Again, injury to the left renal artery or vein can occur while the pancreas is dissected. Often the pancreas, and occasionally the kidneys, are recovered en bloc with the liver and then separated on the back table
• It is unnecessary to perform extensive kidney mobilisation prior to kidney removal, especially in multiple organ recovery. Such retroperitoneal dissection may cause accidental injury to aberrant renal arteries, so causing incomplete perfusion and warm ischaemia of the kidneys (2-4) (level of evidence: 2a)

Table 9: Important considerations in kidney retrieval

• Dissection is carried cephalad and kept as far posterior as possible; the line of dissection is maintained at the level of the paraspinal muscles. Gerota's fascia is kept attached to the kidneys. At the superior poles of the kidneys, the adrenal glands are left intact attached to the kidneys. The kidneys are removed en bloc without identification of the hilar structures
• On the back table, care must be taken to identify aberrant renal arteries, which may originate from the iliac arteries or distal or superior aorta. The aortic segment is left intact. The ureters are examined for length, numbers and size
• It is useful to rewash each kidney until the effluent is free of blood before packaging

•	If the liver is not to be recovered, a double balloon perfusion cannula can be placed in the aorta for selective renal perfusion and a venting catheter is inserted into the lower vena cava to allow venous blood to be washed out
•	Dissection of the kidneys can then proceed with mobilisation of the right colon, exposing the right kidney, the inferior vena cava and lower aorta. Identification and ligation of the inferior mesenteric artery and vein are performed, and the splanchnic nerves are divided, allowing mobilisation of the left mesocolon and exposure of the left kidney. The coeliac axis is identified, ligated and divided
•	Mass clamping of the hepatoduodenal ligament can be performed to minimise flushing of the liver. In a donor < 3-4 years, the surgeon must make sure the aortic cannula does not occlude the renal artery orifices

Improvements in techniques for harvesting organs from non-heart beating donors (NBHDs) has allowed the use of organs that would otherwise not have been considered for transplantation. Reports of the satisfactory function of organs retrieved in this manner have been followed by the development of adequate methods of aortic infusion techniques (11-13). NHB donors accounted for 11,06% in EUROTRANSPLANT and for 6,5% in USA. (12-18).
With the development of multiple organ recovery techniques (19), good co-ordination and co-operation between the various surgical teams involved are essential for the successful retrieval of transplantable organs (2, 19-21). Logistics and programming of organ explantation should routinely be done by the local transplant coordinator.

Recommendations		**GR**
•	Kidneys are the last organs to be recovered in multiple organ recovery. Appropriate placement of the aortic cannula for the cold 'in-situ' flush is essential	C
•	After retrieval of the thoracic organs and liver, and if the pancreas is to be removed, the liver and pancreas should be recovered en bloc and separated on the back table	B
•	In multiple organ recovery, it is essential there is good co-ordination and co-operation between the surgical teams	C

GR = grade of recommendation

2.5.2 The living donor
At present, 20% in EUROTRANSPLANT and 40% in USA of all kidney transplants are performed with living donors (14, 16) (level of evidence: 2a). In countries with low deceased donor rates, over 75% of kidney transplants are with living donors (22).

Most living donors are family members, but there is an increasing number of genetically unrelated donors, who are 'emotionally related', such as spouses or friends. In 2005, in EUROTRANSPLANT, nearly 50% of living donors were not genetically related (42.2%). In the USA, 37.2% were unrelated living donors (14, 16) (level of evidence: 2a).

Ethical guidelines mandate that the living donors have not been coerced and not been paid for their donation. Living donation should be considered a gift of extraordinary value and should be facilitated wherever a suitable donor is available (Table 10) (23-26) (level of evidence: 2b).

Table 10: Advantages of living donation

•	Better results (both long- and short-term) compared to deceased donor grafts
•	Consistent early function and easier management
•	Avoidance of long waiting time for transplantation
•	Less aggressive immunosuppressive regimens
•	Emotional gain to donor
•	Increases globally the kidney transplant rate

2.5.2.1 Evaluation
Evaluation of a potential donor may be performed by an independent physician and consists of a complete history and physical examination, routine laboratory testing, and serological evaluation for Epstein-Barr virus (EBV), herpes virus, cytomegalovirus (CMV), human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBV, HCV). Routine evaluation should also include urinalysis and culture, together with 24-h urine collection for creatinine clearance and protein excretion. A borderline hypertensive blood pressure should be measured on at least three, and as many as 10, separate occasions.

Renal angiography is indicated only if spiral computed tomography (CT) scan with three-dimensional reconstruction or MRI angiography with reconstruction are not available.

Donors are unsuitable for a variety of reasons (Table 11). Potential donors for siblings with diabetes should routinely undergo a 5-h glucose tolerance test and the 24-h urine specimen must be free of proteinuria. Unexplained microscopic haematuria may indicate underlying renal disease. A history of thromboembolism or thrombophlebitis places a potential donor at increased risk of pulmonary embolism and contraindicates donation, as does advanced heart disease or a history of malignant neoplasia. Obesity is a relative contraindication for any potential donor > 30% above ideal body weight.

Table 11: Exclusion criteria for living donors

Absolute contraindications
• Age < 18 years
• Uncontrolled hypertension
• Diabetes mellitus
• Proteinuria (> 300 mg/24 h)
• Abnormal GFR for age
• Microscopic haematuria
• High risk of thromboembolism
• Medically significant illness (chronic lung disease, recent malignant tumour, heart disease)
• History of bilateral kidney stones
• HIV positive
Relative contraindications
• Active chronic infection (e.g. tuberculosis, hepatitis B/C, parasites)
• Obesity
• Psychiatric disorders

GFR = glomerular filtration rate; HIV = human immunodeficiency virus.

Patients with psychiatric disorders should be fully evaluated by a psychiatrist to establish that the donor understands and agrees to the procedure.

2.5.2.2 Choice of kidney

If examination of the donor's vascular supply and drainage system reveals an abnormality, it must be decided whether the risks imposed on the donor or the recipient are too great. When one kidney is smaller or has a minor abnormality, the donor should always be left with the 'better' kidney.

2.5.2.3 Pre-operative management

Pre-operative assessment by the anaesthesiologist and the pain management team is mandatory.

2.5.2.4 Surgical alternatives in live-donor nephrectomy

There are several ways of harvesting kidneys from living donors (Table 12) (11-13, 21, 27-35). The method chosen will depend on the surgeon's experience and preferred choice of operation.

Table 12: Approaches for harvesting kidneys from living donors

Approach	Description
• Classic transperitoneal	Through a midline or through a left or right subcostal incision
• Sub- or supra-costal extraperitoneal	Can be either left- or right-sided
• Dorsal lumbar	Perform incision either underneath the 12th rib, resecting the 12th rib, or above the 12th rib (extraperitoneal, extrapleural)
• Laparoscopic	Can be transperitoneal or retroperitoneoscopic. The transperitoneal approach is more common in the USA and Scandinavia

The operative stages are similar to those in transperitoneal nephrectomy performed for malignant or benign conditions of the kidney. In 2.3% of cases, concomitant splenectomy is needed (11-13, 21, 28-35), due to injuries of the spleen that occur during colon dissection. In addition, the transperitoneal approach is accompanied by a significantly higher rate of intestinal complications, such as ileus (functional or even obstructive).

Removal of the left kidney from a living donor is recommended because of the longer length of the left renal vein (36-38).

Before starting the incision, the donor's diuresis is increased, usually by giving mannitol, 25 g. Arterial spasm may be prevented with externally applied papaverine (39).

Laparoscopic kidney removal (Table 13) is a less traumatic technique, entails less pain, a shorter hospital stay and may encourage more people to consider donation.

Table 13: Special considerations during a laparoscopic procedure

Patient's preparation	During organ harvesting, especially during dissection of the renal pedicle, the patient requires appropriate fluids and a mannitol infusion to maximise renal function during surgery and after transplantation (15-17, 40, 41)
Patient's position on the operative table	Place the patient on the operative table in a left or right position with the kidney bridge. The left kidney is preferred for laparoscopic removal because it has a longer renal vein. On the right side, the liver may make dissection difficult in a transperitoneal approach
Transperitoneal laparoscopic approach	The transperitoneal approach offers more working space. The kidney is approached by dissecting the colon and peritoneum on different lengths. The approach to the renal artery is more complicated due to its position behind the renal vein. However, after detachment from vascular connections, the kidney can be more easily extracted through a lower umbilical incision
Retroperitoneoscopic approach	The retroperitoneal approach allows an easy, initial identification of the renal artery and a direct approach to the branches of renal vein. Its main drawback is the limited space for manoeuvre, which also makes it difficult to use endobags for a quick kidney extraction

2.5.2.5 Post-operative care

Adequate post-operative analgesia is crucial in preventing post-operative complications, such as atelectasis and pneumonia (20, 21). Antibiotic prophylaxis should also be given. Subcutaneous heparin, the continuous use of leg stockings and sequential compression devices should be prescribed to prevent deep venous thrombosis of the lower limbs. Most patients tolerate oral feeding by post-operative day 2 or 3, and the donor can be discharged between post-operative days 2 to 6. Renal function should be assessed periodically after operation. Although donors experience a 25% increase in serum creatinine level, the creatinine level should return to near baseline within 3 months.

There are no convincing data to suggest that living donors are at increased long-term risk because of kidney donation. Nevertheless, ongoing periodic long-term follow-up evaluation is recommended for donors. This can be performed by the donor's personal physician (14-17, 40-43) (level of evidence: 2a).

Recommendations	**GR**
• The use of living donors has been associated with higher success rates than seen with deceased donor donation. Living donation allows some patients to avoid long waiting times and even dialysis	B
• An independent assessment of the donor's renal function by a nephrologist or a specialised team is mandatory in all cases	B
• It is advisable to obtain a psychiatric or independent medical evaluation of the donor's motivation, fitness, and his ability to understand the risks of the operation	B
• It is the surgeon's responsibility to ensure that the donor is medically, as well as psychologically suitable, for the procedure; the donated organ is healthy; and the expectation of success in the recipient is reasonable	B
• The donor should always be left with the 'better' kidney. Kidney removal through a transperitoneal approach has a higher number of splenic and intestinal complications compared with other surgical alternatives	B
• Open-donor nephrectomy should be performed by an extraperitoneal approach through a subcostal or dorsal lumbotomy incision	B

•	Laparoscopic donor nephrectomy (either trans- or retro-peritoneal) should only be performed by those trained in the procedure	B
•	Hand-assisted laparoscopic donor nephrectomy minimises warm ischaemia time compared to classic laparoscopic procedures	B

GR = grade of recommendation

2.5.3 References

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2.6 Organ preservation

2.6.1 Kidney storage solutions

There is no agreement on which of the mechanisms listed in Table 14 is most important for post-ischaemic renal graft function (1-6). No storage solution combines all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended. Today, Celsior-solution, UW- (University of Wisconsin) and HTK- (histidine-tryptophane-ketoglutarate) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures (7-10) (level of evidence: 1b). For living donors, in whom a long cold ischaemia time is not expected, perfusion with crystalloid solution (e.g. Ringer-lactate) is sufficient.

Table 14: Aims of modern kidney storage solutions*

• Control of cell-swelling during hypothermic ischaemia
• Maintenance of intra- and extra-cellular electrolyte gradient during ischaemia
• Buffering acidosis
• Providing energy reserve
• Minimising oxidative reperfusion injury

**From references 1-6.*

2.6.2 Methods of kidney preservation

There are two methods of kidney preservation:

- Initial flushing with cold preservation solution followed by ice storage.
- Continuous pulsatile hypothermic machine-perfusion (clinical relevance for non heart-beating donors and marginal donors).

2.6.3 Duration of organ preservation

The duration of cold ischaemia should be as short as possible. Kidneys from the elderly (> 55 years) and marginal donors are more sensitive to ischaemia than young kidneys (level of evidence: 1b). Organ preservation relies mainly on hypothermia, which lowers the metabolic rate, conserves stores of adenosine triphosphate, and prevents formation of oxygen-free radicals during the reperfusion phase.

Recommendations	GR
• University of Wisconsin (UW)-solution and histidine-tryptophane-ketoglutarate (HTK)-solution are standard storage solutions and equally effective for both multiorgan-donors and kidney-only donors	A
• Celsior-solution seems to be equally effective	B
• Keep cold and warm ischaemia times as short as possible for any renal transplant	A

GR = grade of recommendation

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3. KIDNEY RECIPIENT

Kidney transplantation prolongs life, reduces morbidity, improves quality of life, enables social and medical rehabilitation and reduces the costs associated with the medical care of patients with ESRD.
Kidney transplantation is a surgical procedure, with inherent risks due to anaesthesia and the surgical procedure itself. In addition, the need for continuous immunosuppressive therapy may lead to immunosuppression-related side-effects.

The pre-transplant evaluation evaluates potential contraindications and risk factors for transplantation (e.g. malignancy, ongoing infection) (level of evidence: 2b).

Recommendation	GR
• Careful pre-operative work-up of all transplant candidates is mandatory to improve organ and patient survival in the post-transplant period. The work-up should be repeated regularly	B

GR = grade or recommendation

3.1 Pre-transplant therapy

3.1.1 Abnormal urogenital tract

In patients, whose ESRD is caused by either a congenital (i.e. posterior urethral valve, spina bifida, prune belly syndrome, vesico-renal reflux, bladder exstrophy, VATER syndrome) or an acquired malformation (shrunken or neurogenic bladder, neurogenic) of the lower urinary tract, the abnormality should be corrected before transplantation (1-4).

Avoid ureteral implantation in a fibrotic, thickened, bladder wall (e.g. following an urethral valve) because of the high risk of surgical complications and/or graft loss (1). In low-compliance bladders, pharmacological therapy (e.g. parasympathicolysis), with or without intermittent self-catheterisation, is necessary. If these methods fail, bladder augmentation is recommended. If catheterisation is not possible, supravesical urinary diversion is crucial.

Anatomical or functional urological disorders do not seem to change the outcome of renal transplantation (level of evidence: 3).

3.1.2 Urinary diversion

In patients with sphincter insufficiency (e.g. neurogenic bladder) or absent bladder, supravesical urinary diversions must be performed, such as conduits or continent catheterisable pouches. Artificial sphincters may be an alternative. In low-compliance bladders with intact sphincters, both bladder augmentation and continent pouches are successful alternatives (4-9).

Most authors prefer to perform a supravesical urinary diversion at least 10-12 weeks before transplantation (6, 8). Bladder augmentation or conduit is possible following transplantation (6). Patients with conduits, augmented or abnormal bladders have an increased risk of urinary infection (1, 4-6).

Results can be similar to those in the general population (7, 9-12) (level of evidence: 3).

3.1.3 Indications for pre-transplant nephrectomy

Depending on the indication (Table 15), nephrectomy can be done by either an open or laparoscopic approach (level of evidence: 3-4).

Table 15: Indications for pre-transplant nephrectomy

Autosomal-dominant polycystic kidney disease (ADPKD)
• Unilateral or bilateral nephrectomy is necessary if there is not enough space for the transplant kidney, or if there are complications, such as cyst infection, cyst rupture with/without haematuria, pain, or abdominal girth
• Nephrectomy can be done before transplantation or simultaneously with similar complication rates and outcomes (2, 13, 14)
Medically refractory hypertension
• Bilateral nephrectomy usually results in less antihypertensive medications (15). It has become rare due to improved control of hypertension with better dialysis and drugs

Chronically infected kidneys		
Suspected renal or urothelial cancer		
Urolithiasis		
•	No strong evidence for removal of native kidneys in urolithiasis	
•	Nephrectomy is necessary if there is a possible risk of infection due to stones	
Recommendations		**GR**
•	In abnormal urogenital tract, meticulous pre-transplant work up is necessary, with urodynamics being the key investigation	B/C
•	If pharmacological therapy or intermittent catheterisation fails or is not possible, urinary diversion is necessary using catheterisable pouches, conduits or cystoplasties	B/C
•	ADPKD with insufficient space or complications, chronic infections, or kidneys with suspected tumour growth have to be removed either pre-operatively or concomitant with transplantation	B/C

GR = grade of recommendation

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3.2 Selection and refusal criteria

3.2.1 Contraindications

3.2.1.1 Malignancy

Active malignancy is a contraindication for transplantation because immunosuppressive therapy may aggravate underlying malignancy, jeopardising the patient's life and long-term success of the transplant (1-3). Patients with a history of malignancy should be cured (see Chapter 8 - Malignancy).

3.2.1.2 Infection

Infections can be a major cause of morbidity and mortality in transplanted patients, especially under intense immunosuppressive therapy. As part of the pre-transplant work-up, carry out screening for infections to exclude any active infections, which might jeopardise the immediate outcome post transplant (1-3). In contrast, chronic infection does not cause an immediate post-operative risk. If chronic infection is detected, counsel the patient and treat it before transplantation or take prophylactic measures after transplantation. Screening for infections also documents the recipient's infectious status in case of disease transmission from the donor. In cases of previous negative serology for CMV, HBV, HCV and HIV recipients, serology should be repeated at the time of transplantation. A record of the viral status before transplantation enables graft transmission of disease to be firmly excluded. Finally, the recipient's infectious status may have implications for the allocation of organs (level of evidence: 3).

If the patient's history or physical examination suggests an underlying infection, a thorough examination should be instituted, which may involve physicians from other subspecialties, such as an ear, nose and throat specialist, dentist, dermatologist, urologist and gynaecologist, to firmly rule out infectious foci (1-3) (level of evidence: 3).

Important infections screened prior to transplantation are HBV, HCV, HIV, tuberculosis (TB), cytomegalovirus (CMV), and Treponema pallidum (1-3). Testing of HBV and HCV serology is particularly important, because viral hepatitis is the major cause of liver disease after renal transplantation and contributes to post-transplant morbidity and mortality (4, 5, 6) (level of evidence: 3). A liver biopsy may be needed to assess disease status in patients positive for HBV or HCV before transplantation. Consider antiviral therapy before transplantation according to current guidelines (7, 8, 9) (level of evidence: 3).
The serological CMV status of all recipients should be determined (1-3) (level of evidence 3). Current immunosuppressive regimens are associated with a high incidence of potentially life-threatening CMV disease (4, 10) that is, however, preventable with the appropriate prophylactic strategy (level of evidence: 1a).

HIV screening is recommended because active HIV disease is a contraindication for transplantation (1-3). However, retrospective studies show that renal transplantation can be successful in well-controlled (no detectable viral load) and treated HIV-positive recipients (3) (level of evidence: 3).
A history of TB is important because adequate preventive measures (e.g. isoniazid prophylaxis; 11, 12) will avoid reactivation of TB under heavy post-transplant immunosuppression (level of evidence: 1a). Screening for TB requires a careful history and chest X-ray (1-3) (level of evidence: 3).

Screening for T. pallidum has been previously recommended (1, 2). However, due to the low incidence of disease, it is not strongly recommended for all potential transplant candidates. A Treponema haemaglutination (TPHA)-test may be performed in populations with a higher risk for disease (level of evidence: 3).

Screening for Epstein Barr virus (EBV) has been suggested in children and young adults (13), because of their higher risk for the development of EBV-related lymphoproliferative disease. General EBV screening is not recommended (level of evidence: 3)

Recommendations	GR
• Active infection, which may exacerbate after transplantation causing life-threatening infection, is a contraindication to transplantation	B
• Carry out screening for viral and bacterial diseases in all transplant candidates Screen all patients for HBV, HCV, HIV and CMV and TB (history and chest X-ray)	B
• Routine screening examination of all patients in all subspecialties is not necessary	B

GR = grade of recommendation

3.2.1.3 Other contraindications for transplantation

Transplantation should be offered to patients with potential for long-term survival of the graft because of the scarcity of organs, the complexity of the transplant procedure, and increased mortality associated with the transplant procedure itself.

A short life expectancy and conditions (e.g. severe psychiatric disease) that interfere with compliance are not acceptable risks for long-term success of transplantation. If there is non-compliance, a careful psychological examination should try to identify the underlying cause (14) and if possible institute an adequate treatment (15). Non-compliance is not a lifelong determinant of a personality and re-evaluation may be needed.

Recommendation	GR
• In severe co-morbidity or non-compliance, a thorough and individual assessment should be performed	C

GR = grade of recommendation

3.2.2 Co-morbidity

Due to the inherent risks of the surgical procedure, anaesthesia and post transplant immunosuppressive therapy a careful evaluation of potential transplant recipients is very important, particularly a cardiovascular work-up to reduce early graft failure due to technical problems and to improve patient survival in the post-transplant period (1-3).

3.2.2.1 Cardiac disease

Death with a functioning kidney allograft occurs frequently in kidney-transplanted patients, with cardiac death being the most important cause (16). Nevertheless, uraemic patients with cardiovascular disease are more likely to survive with a renal transplant compared to dialysis (17, 18). However, patients with cardiac disease have a higher peri-operative risk (19, 20). All candidates should therefore be given a careful history and physical examination for cardiac disease, including an electrocardiogram and chest X-ray (21) (level of evidence: 3).

An additional, extensive, cardiac work-up is recommended for patients with a history of coronary heart disease, severe peripheral artery disease, or a history of stroke or severe occlusive cerebrovascular disease, and a long history of renal insufficiency/dialysis (22, 23), as well as for elderly and/or diabetic patients (22, 24, 25) (level of evidence: 3).

The work-up includes (22, 23):

- Echocardiography to detect valvular disease, cardiomyopathy, and systolic and/or diastolic left ventricular dysfunction (26).
- Exercise electrocardiogram and/or exercise thallium scintigraphy or stress echocardiography in patients with a low exercise capacity (22, 23).
- Coronary angiography in every suspicious case, especially in dialysis patients who are elderly and/or diabetic, or in patients with a long history of renal disease (27).

Revascularisation, either surgical, or by coronary angioplasty, should be performed in every suitable transplant candidate (18, 24) before transplantation (level of evidence: 3)

Recommendations	GR
• Pre-transplant work-up should focus on the presence of cardiac disease	B
• In patients with a high risk of cardiac disease, an extensive work-up is strongly recommended to firmly rule out coronary artery disease	B
• Perform any revascularisation before transplantation	B

GR = grade of recommendation

3.2.2.2 Peripheral artery disease, cerebral occlusive vascular disease

Peripheral artery disease is common in uraemic patients (28). In potential kidney transplant recipients, very

severe pelvic vessel disease may prohibit transplantation, be a significant cause of technical graft failure, and may enhance the risk of amputation. Cerebral vascular occlusion may lead to post-operative morbidity and mortality (29, 30).

Evaluate the patient carefully for signs and symptoms of vascular occlusive disease. Pelvic radiography should be done routinely before transplantation (31, 32). If there is vascular calcification, signs and symptoms or risk factors (e.g. age, diabetes, length of time on dialysis) of vascular occlusive disease, perform a thorough work-up, including duplex ultrasonography of the peripheral and cerebral arteries (33), and/or non-contrast enhanced abdominal-pelvic CT scan. In selected patients, angiography and pre-transplant arterial repair can be indicated. Avoid contrast-enhanced magnetic resonance imaging (MRI) because of the risk of nephrogenic systemic fibrosis (34) (level of evidence: 3).

Recommendation	**GR**
• During pre-transplant work-up, special attention should be paid to iliacal, peripheral and cerebrovascular disease. Appropriate diagnostic and therapeutic measures are recommended	C

GR = grade of recommendation

3.2.2.3 Diabetes mellitus

Patients with diabetes mellitus have an increased mortality and reduced long-term graft outcome compared to non-diabetic patients following kidney transplantation (35). Nevertheless, diabetes mellitus itself is not a contraindication for kidney transplant (1-3). Furthermore, a kidney-only transplant or a combined kidney-pancreas transplant will reduce the long-term morbidity and mortality of uraemic diabetic patients compared to dialysis (36, 37) (level of evidence: 3).

Thus, kidney transplantation should be considered in every diabetic uraemic patient who has no other severe contraindication, especially cardiovascular disease. In patients with diabetes type I, a combined kidney-pancreas transplant is preferred because it improves blood glucose control and slows progression of cardiovascular disease (38, 39) (evel of evidence: 3).

Because there is an exceptionally high incidence of cardiovascular disease in diabetic dialysis patients (21-23), it is usually necessary to exclude patients with a high vascular risk using peripheral angiography or non-invasive imaging procedures (e.g. CT scan) (27). Bladder neuropathy is a common complication in diabetic patients (40) and a urological clinical work-up should be performed. In selected patients, an urodynamic examination is needed (level of evidence: 3).

Recommendation	**GR**
• Patients with diabetes mellitus should be transplanted. They require an extensive pre-transplant work-up	B

GR = grade of recommendation

3.2.2.4 Obesity

Overweight patients have a higher incidence of surgical and non-surgical complications (41, 42). Weight is a traditional risk factor for diabetes, hypertension and cardiovascular disease. However, renal transplantation provides a better survival and better quality of life in overweight dialysis patients (43, 44) (level of evidence: 3). There is not enough evidence to recommend exclusion based on body mass index (BMI).

Recommendation	**GR**
• Obesity itself is not a contraindication for transplantation. However, a thorough pre-transplant evaluation and attempt to reduce weight are recommended	C

GR = grade of recommendation

3.2.2.5 Coagulopathies

Coagulation disorders have a negative impact on post-transplant graft survival, leading to early graft thrombosis or post-transplant thrombotic complications (45, 46). Early post-transplant anticoagulation may prevent thrombosis and early graft loss (47, 48). As a consequence, a pre-transplant work-up should include the diagnosis of coagulopathies, especially in patients with recurrent shunt thrombosis or with a history of thrombotic events. In these patients, a careful pre-transplant assessment is mandatory, including ATIII, protein C, activated protein C resistance (Factor V Leiden), protein S, and anti-phospholipid antibodies (level of evidence: 3).

Patients on anticoagulant treatment, e.g. warfarin, acetylsalicylic acid, clopidogrel, are not excluded from transplantation. During surgery, special precautions for anticoagulant use are needed.

Recommendation	GR
• A careful examination of coagulopathies in patients at risk in order to prevent early post-transplant thrombotic events is recommended	C

GR = grade of recommendation

3.2.2.6 Other diseases with potential influence on post-transplant outcome

Some conditions or diseases may follow an aggravated clinical course after transplantation due to immunosuppressive therapy and/or may place the transplanted kidney at a higher risk for complications (1-3). Important examples are diverticulosis, with or without previous episodes of diverticulitis, cholecystolithiasis and hyperparathyroidism. Decisions for pre-transplant treatment should be made by a multidisciplinary team on an individual basis with appropriate patient counselling. (Level of evidence 4)

Mental retardation and psychiatric diseases are not necessarily contraindications for transplantation (1-3). If the patient is able to understand the procedure and can adhere to the procedures and medication required, such patients are eligible for transplantation (level of evidence: 4).

Recommendation	GR
• Diseases that might influence post-transplant course should be identified during pre-transplant work-up and if possible treated before transplantation	C

GR = grade of recommendation

3.2.3 Age

Although there is no controversy about the fact that a kidney transplant offers improved survival and quality of life in younger patients with ESRD, an ongoing debate exists about kidney transplants in the elderly.

Reduced mortality in patients over 65 years has been shown in transplanted patients compared to patients on the waiting list (35, 36) and reasonable outcomes have been reported for elderly transplant recipients (49, 50) (level of evidence: 3). However, a prolonged waiting time in this patient subgroup significantly decreases the beneficial clinical outcome and socio-economic advantages of transplantation (51, 52) Every effort should be taken to reduce waiting times in the elderly (over 65 years). Elderly transplant patients should be enrolled in special programmes such as the Eurotransplant (ET) Senior programme (50), as well as applying for living-donor transplantation (level of evidence: 3).

In elderly dialysis patients selected for kidney transplantation, special attention must be paid to concomitant cardiovascular disease and possible pre-existing cancer (53). Patients should be informed about the potential hazards of transplantation, including a high fatality rate in the first year after transplantation (and infection during the first year post-transplant (49, 50, 53-56) (level of evidence: 3). If there are any signs of age-related dementia, a psychological evaluation should be instituted.

Recommendation	GR
• Although age itself is not a contraindication for transplantation, a thorough pre-transplant evaluation is needed. A careful risk-benefit evaluation must be performed and the patient should be counselled on the increased risks associated with age	B

GR = grade of recommendation

3.2.4 Recurrence risk (original renal disease)

An histological recurrence of original renal disease is common in a transplanted kidney. Despite high recurrence rates in some diseases, overall graft loss due to recurrence is less than 10% after 10 years (57, 58). Higher recurrence rates have occurred in living related donors and living donation should therefore be critically discussed, especially in diseases with early and very high recurrence rates (level of evidence: 3).

Some rare renal diseases with a high recurrence rate, which can lead to an immediate graft loss, are contraindications for transplant. They include light-chain deposit disease (LCDD), primary oxalosis, and anti-glomerular basement (anti-GBM) antibodies) (1-3). However, transplants may still be possible in some circumstances:

- Patients with anti-GBM disease can be given a transplant after disappearance of anti-GBM antibodies (1-3) (level of evidence: 3).

- In patients with primary oxalosis, combined liver-kidney transplantation is recommended (1-3) (level of evidence: 3).
- In patients with amyloidosis or LCDD, no treatment guidelines exist. In this very rare group of patients, case reports and small case series describe successful chemotherapy or autologous stem cell transplantation, with or without kidney transplantation (59-61) (level of evidence: 3).

In patients with systemic diseases (e.g. lupus, vasculitis, haemolytic uraemic syndrome), the underlying disease should be treated and the patient should be in remission before transplantation (1-3) (level of evidence: 3)
For most patients with glomerulonephritis, no special precautions are recommended (1-3). Focal and segmental glomerulosclerosis (FSGS) may recur early after transplantation (62, 63) and may be treated with plasmapheresis and/or with anti-CD20 antibody (rituximab) (64, 65) When a previous graft has been lost because of recurrent glomerulonephritis, especially FSGS, the patient must be counselled on the higher risk of graft failure in a second transplant. However, successful long-term outcomes have occurred in these patients. (62, 63) (level of evidence: 3).

Recommendations	**GR**
• Recurrence of the original disease is common, but graft loss due to recurrence is infrequent	C
• Only a few rare diseases with a high recurrence rate leading to early graft loss are a contraindication for renal transplant	C
• Patients with the risk of recurrent diseases should be counselled before transplantation, especially before living related kidney transplant	C

GR = grade of recommendation

3.2.5 Patients with a previous transplant

Assess patients with a previous graft loss carefully for malignancy, cardiovascular disease (1-3) and for increased immunological risk because of the development of antibodies against the first graft (66). Gradually discontinue immunosuppression following graft failure, as continuous immunosuppressive therapy has a higher risk of complications under renal replacement therapy (67, 68) (level of evidence: 3). If the graft becomes symptomatic, perform graft nephrectomy immediately (69). Graft embolisation (70) may be an alternative. However, prophylactic transplantectomy does not seem to be beneficial (71-73). Take appropriate measures to avoid repeated alloantigen mismatches (level of evidence: 3).

Patients with a previous non-renal organ transplant, who develop ESRD (74, 75), also benefit from renal transplantation, as there is a high risk of severe complications with a combination of ESRD and continuous immunosuppressive therapy (76) (level of evidence: 3) . Work-up should pay special attention to malignancy, cardiovascular disease, potential immunisation, and potential graft dysfunction of the previously transplanted organ, which may therefore require a combined transplant procedure (level of evidence: 3).

Recommendation

- Pre-transplant work-up for patients with retransplantation or previous non-renal transplantation should focus on the immunological risk, including a thorough analysis for the presence of anti-HLA antibodies

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3.3 Transplantation in pregnancy

3.3.1 Planning pregnancy

Chronic renal failure is often associated with sexual dysfunction and infertility. After kidney transplantation, sex life and fertility are improved (1). Both male and female patients should be counselled about the possibility of pregnancy. Ideally, pregnancy should be planned at a time of good general and graft health, usually not earlier or later than 1-2 years after transplant (2). In pregnancy occurring some years after transplantation, there is a risk that some chronic rejection and/or some deterioration of renal function may have developed.

If graft function and immunosuppressive therapy are stable, and there is no sign of rejection, hypertension, proteinuria, hydronephrosis or chronic infection, there is no significant difference in outcome between early, recommended, or late pregnancies (3) (level of evidence: 2a). Hydronephrosis makes pregnancy riskier because of the increased possibility of infection and lithiasis, which may also worsen in the last trimester. Early detection of pregnancy is important so that monitoring and adjustment of immunosuppressive therapy can begin as soon as possible.

Recommendations	GR
• Pregnancy should be planned at a time of good general and graft health, when renal function and immunosuppressive therapy are stable and there is no sign of rejection, hypertension, proteinuria, hydronephrosis or chronic infection	B
• The second post-transplant year is the ideal period	B

GR = grade of recommendation

3.3.2 Graft survival

Recently, the pregnancy rate in the kidney-transplanted population has increased from 2% to 5%. Successful gestations are common in female organ transplant recipients (4) (Table 16).

Table 16: Factors that may affect a kidney graft during pregnancy

• Haemodynamic changes
• Hypertension
• Impairment of renal function (5-10) (level of evidence: 2a)
• Rejection (11)
• Urinary tract infections

Pregnancies in transplanted women are often unproblematic, but these patients should always be considered high risk and require shared care by an obstetrician, nephrologist and a urologist.

Recommendations	GR
• After kidney transplantation pregnancy is possible and well tolerated for most patients with normal graft function	B
• However, pregnant transplanted women always must be considered at high risk and their care requires the co-operation of the obstetrician, nephrologist and urologist	B

GR = grade of recommendation

3.3.3 *Care during pregnancy*

The care of a pregnant transplanted patient should focus on the risk factors mentioned in Table 16. This includes checking for bacterial urinary tract infection with monthly urine cultures and always treating bacteriuria, whether symptomatic or asymptomatic. Antibiotics agents should be chosen from the penicillin and cephalosporine families to avoid fetal and renal toxicity. Every urological endoscopy requires antibiotic protection. Viral infections may be transmitted to offspring. If this is CMV, the baby may be mentally retarded. Amniotic culture will reveal any fetal infections (12).

Recommendation	GR
• Care during pregnancy should focus on control of proteinuria, hypertension (pre-eclampsia affects 30% of patients), renal function, rejection and infection	B

GR = grade of recommendation

3.3.4 *Immunosuppressive treatment*

The common immunosuppressive treatment used during pregnancy is cyclosporine, with or without azathioprine and prednisone (6, 13). These drugs pass the placental barrier but apparently do not increase the risk of teratogenicity. Blood cyclosporine levels may change, and usually decrease, especially during the third trimester because of increased volume distribution and pharmacokinetic changes. Its dosage should usually be augmented. Recent papers suggest that the new drug tacrolimus (14, 15) (level of evidence: 3, 2b) used in kidney, heart and liver transplantation might also be safe. There are only sporadic reports on the effects of mycophenolate mofetil (MMF), which, like sirolimus, is contraindicated due to teratogenicity (16).

Recommendations	GR
• Cyclosporine and tacrolimus do not seem to increase the risk of teratogenicity and they are currently used with or without steroids and azathioprine	B
• Treatment with mycophenolate (mycophenolate mofetil or mycophenolate sodium) or m-TOR- Inhibitors (sirolimus or everolimus) is not recommended	B

GR = grade of recommendation

3.3.5 *Follow-up*

Rates of spontaneous (14%) or therapeutic (20%) abortions in transplanted women are similar to those in the general population. Although a vaginal delivery is not mechanically impaired by an abdominal graft, pre-term delivery and a high rate (50%) of Caesarean sections are observed, due to a high incidence of prematurity (uncontrolled hypertension, fetal distress, rupture of membranes weakened by steroid use). About 20% of babies have a low birthweight (mean birthweight 2.5 ± 0.67 vs normal birthweight 3.5 kg ± 0.53) (17, 18), but congenital abnormalities are no higher than in the general population. Breastfeeding is not suggested because of the baby's risk of ingesting immunosuppressive agents. A close follow-up of the mother in the first three post-partum months is recommended, including weekly renal function tests. Delay vaccinations until the infant is 6 months old.

There are few data on the growth, long-term outcome, or adult life of children born from kidney-transplanted mothers. Offspring are often born prematurely and have a reduced birthweight. Long-term studies on fetal exposure to immunosuppressive therapy have only recently begun. No other important data exist at present. Children of fathers in immunosuppressive treatment following kidney transplantation are clinically not different from those of the general population. They are aborted less often than fetuses of kidney-transplanted mothers. However, if the father is affected by hereditary disease, there is a higher risk of transmission.

Recommendations	GR
• If there is no premature condition or fetal distress, vaginal delivery can be considered	B
• Breastfeeding is not recommended because of the potential risk of ingesting immunosuppressive agents	B

GR = grade of recommendation

3.3.6 *References*

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4. TRANSPLANTATION TECHNIQUES

4.1 Transplant preparation and transplant techniques in adults.

Transplant preparation is a crucial step in the transplantation process and should not be neglected. Key points of transplant preparation are listed in Table 17. The transplant procedure in adults, with special considerations, is detailed in Table 18.

Table 17: Transplant preparation

Kidney	
•	Place the kidney on a sterile iced bed
•	Check for the absence of renal tumours
•	Tie all that is cut near the hilus (lymphostasis)
Vein	
•	The right kidney should be removed, together with the infra renal vena cava for lengthening the renal vein on the back table (1)
Artery	
•	Preserve the aortic patch and check the intima of the renal ostium
•	In severe atheroma in the ostium, remove the aortic patch
•	In multiple arteries, back table reconstruction could be necessary (2, 3)
Ureter	
•	Preserve peri-pyelic and proximal peri-ureteral fat in the 'golden triangle'
•	Check for double ureter
Transplant biopsies	
•	Use 16G or 18G automatic single-use needle
•	Systematic in some centres because it can be very important to follow the long-term histological modifications of the transplant

Table 18: Transplant technique

Transplant technique in adults	
Approach	
•	Extra peritoneal approach of one iliac fossa
•	Transplantation is possible either into the contralateral or ipsilateral iliac fossa
•	Lymphostasis with clips or ligatures to avoid lymphocele is mandatory
•	Total mobilisation of the external iliac vein avoids traction on the venous anastomosis (sometimes ligation of the internal iliac vein is necessary particularly for right transplant with a short vein)
•	Minimal dissection of the iliac artery
Vascular anastomosis	
•	Generally external iliac vessels are used; avoid atheromatous plaques
•	Choose the sites of vascular anastomosis according to the length of each vessel to avoid plication or traction
•	Both anastomoses are performed with two halves of running non-absorbable monofil 6x0 or 5x0 sutures
•	Internal iliac artery should not be used except in specific situations
Ureteral anastomosis	
•	Extravesical implantation at the antero-lateral surface of the bladder is the method of choice. Suture the ureter to the bladder mucosa using two halves of running absorbable 6x0 or 5x0 sutures. This technique gives better results than open implantation to the bladder (4, 5)
•	A double J-stent may be placed to protect the anastomosis, particularly in cases of tricky anastomoses. Several transplant groups use a double J-stent routinely (6-8) and remove it 2-4 weeks later (level of evidence: 2b)
•	The uretero-ureteral anastomosis is an alternative to a very short or poorly vascularised transplant ureter. It is also used for a third transplant or in children (9). A double J-stent is absolutely necessary in these cases (level of evidence: 3)
Special considerations	
Kidneys taken from children weighing < 15 kg	
•	In adults, en-bloc transplantation should be performed, including the aorta and the inferior vena cava
•	The two ureters are anastomosed in double pant using the extra-vesical technique

Vascular problems in the recipient
• If the iliac arteries do not allow clamping, endarterectomy or a simultaneous vascular prosthesis has to be performed (10)
• If a prosthetic replacement has been previously carried out, implant the renal artery into the prosthesis using a punch perforator (11)
• If iliac vein and/or vena cava are thrombosed, native renal vein or superior mesenteric vein can be used. However, in most cases, transplantation must be stopped
Paediatric recipient
• Large kidneys must be placed in a higher position towards the lumbar fossa, using the aorta or the right common iliac artery and the inferior vena cava
• Iliac fossa is an option for young recipients (12, 13) (level of evidence: 3)

Recommendations	**GR**
• It is essential not to neglect transplant preparation. This is a crucial step in the transplantation process	C
• Take care with lymphostasis into the recipient and during the graft preparation	C
• Vascular anastomosis sites should take into account the differences in vessel length	C
• Double J-stent may be used routinely	C
• Check the arterial and venous status before transplant	C
• Iliac fossa may be an alternative in children less than 20 kg provided the graft is small enough	C

GR = grade of recommendation

4.2 Early complications

4.2.1 General complications

4.2.1.1 Wall abscesses (5%)

These are more common when the recipients are obese or old. Risk factors include diabetes, haematoma, obesity, rejection or over-immunosuppression (14, 15). Abscesses can be prevented by minimising electro-coagulation and using subcutaneous aspirational drainage in obese patients.
A superficial abscess can be treated with a simple opening of the wound, while a deep abscess requires surgical drainage. It is important to look for urinary fistulae.

4.2.1.2 Haemorrhage

Risk factors include acetylsalicylic acid, poorly prepared transplant hilus, multiple renal arteries, renal biopsies and hyper-acute rejection (HAR) (16-18). A large haematoma or active bleeding requires surgical drainage. Following drainage, the uretero-vesical anastomosis must be checked and a double J-stent may be inserted.

4.2.1.3 Haematuria

After transplant biopsy, look for arterio-venous fistula (AVF) (19). Selective percutaneous embolisation is necessary for large AVF and for recurring haematuria. Clotting may cause ureteral obstruction, increasing the risk of haematuria. Dialysis may be necessary if ureteral stenting or percutaneous nephrostomy are ineffective.

4.2.1.4 Incisional hernia (3-5%)

Risk factors include obesity, diabetes, haematoma, rejection and finally m-TOR inhibitors. Treat in a similar way to a ‘classical‘ incisional hernia with or without synthetic mesh (14, 20, 21).

4.2.2 Urinary fistulae

Urinary fistulae are the most common early complication. They occur in 3-5% of cases in which a double J-stent has not been used (22-24). They can occur on the ureter, bladder or parenchyma. The most frequent cause is ischaemic necrosis of the ureter (23, 25).

4.2.2.1 Management

If it is possible to localise the fistula, it is worth trying nephrostomy and/or a vesical catheter and double J-stent. Stented re-implantation is possible if necrosis is very distal and the ureter is long enough. Otherwise, uretero-ureteral anastomosis is performed using the patient’s original ureter (26). Vesical fistulae can be treated by suprapubic or transurethral catheter. Calyceal fistulae may be treated by double J-stent and vesical catheter. In most cases, polar nephrectomy and omental plasty are necessary (27).

Recommendations	GR
• Use a short ureter and keep the peri-ureteral fat around the hilus (28)	C
• Avoid ligature of polar artery because of the risk of parenchymal and ureteral necrosis	C
• Prophylactic use of double J-stent remains controversial	C

GR = grade of recommendation

4.2.3 Arterial thrombosis

The incidence of arterial thrombosis is 0.5% in the first post-operative week. Risk factors include atherosclerosis, unidentified intimal rupture, poor suture technique, kinking if the artery is longer than the vein or the anastomosis is incorrectly sited, multiple arteries (29) and paediatric transplants (30-32). It should be suspected if there is primary non-function or sudden anuria. It is diagnosed by Doppler or technetium scan and confirmed by CT scan.

4.2.3.1 Treatment

Surgery is always necessary. A radiological thrombectomy may be carried out successfully within the first 12 h. However, tolerance to warm ischaemia is poor and most transplants have to be removed.

Recommendations	GR
• Importance of procurement technique quality	C
• Preserve when possible the aortic patch; otherwise, use a punch perforator to create a large arterial opening	C
• Look for a possible intimal rupture before performing anastomosis	C
• Avoid plication of the artery	C

GR = grade of recommendation

4.2.4 Venous thrombosis

Venous thrombosis is rare, occurring in 0.5% of kidney transplants in adults and in 2.5% in paediatric patients (32, 33). It is suspected by primary non-function, haematuria or anuria and is diagnosed by Doppler or technetium scan. Salvage thrombectomy has a very poor success rate and transplantectomy is often necessary.

Recommendations	GR
• Lengthen the right renal vein with the infra renal vena cava	C
• Carry out a large venous anastomosis	C
• Avoid post-operative drop in blood pressure	C
• Check for hypercoagulation or Leiden factor V mutation if there is a history of thrombosis	C

GR = grade of recommendation

4.3 Late complications

4.3.1 Ureteral stenosis

The renal calyces and pelvis are dilated and there is often an elevated creatinine level. These stenoses occur in 5% (range, 2-7.5%) of transplants (34, 35). They can present late between 1 and 10 years' post transplant (36). There are three causes of ureteral dilatation:

- Vesical high pressure with thickened bladder wall or urinary retention, which is treated by bladder drainage
- Vesicorenal reflux, which is not an obstruction
- Ureterovesical stenosis due to scar formation and/or poor surgical technique. These comprise 80% of ureteral stenoses. Most occur during the first year post transplant, although the risk of occurrence increases with time to 9% of transplant patients at 10 years.

Risk factors include multiple arteries, donor's age, delayed graft function, and CMV infection (34).

Initial treatment involves percutaneous drainage and checking renal function to see if it has improved. Imaging should then be done to determine the level of stenosis, degree and length. Further treatment depends on the level of stenosis, degree and delay of occurrence. This can be endoscopic, either transurethral or percutaneous. The outcome of dilatation is better when the stenosis is early, distal and short (37-41). Treatment can also be with open surgery using an uretero-ureteral anastomosis to the patient's ureter or a vesicopyelostomy.

Recommendations	GR
• Use a short and well-vascularised ureter, surrounded by peri-ureteral fat	
• Do not narrow the anastomosis and the antireflux tunnel	
• Use of a double J-stent remains controversial	
• Yearly routine echography	

GR = grade of recommendation

4.3.2 Reflux and acute pyelonephritis

Acute pyelonephritis is a rare complication (42, 43). Reflux in the renal cavity is more common (44). Reflux is found in up to 30% of cases after Leadbetter and in 80% after Lich-Gregoire if the submucosal tunnel is short and in 10% if the tunnel is long. In lower urinary tract infections, the risk of acute pyelonephritis is 80% with reflux and 10% without reflux. Every reflux complicated by acute pyelonephritis should be treated with an endoscopic injection. This has a success rate of 30-53% (45). If this fails, try using an uretero-ureteral anastomosis if the native ureter is not refluxive, or an ureterovesical re-implantation with a long tunnel if the original ureter is refluxive or non-usable.

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Recommendations
• The anti-reflux tunnel for the uretero-vesical anastomosis should be 3-4 cm long
• Avoid lower urinary tract infections

GR = grade of recommendation

4.3.3 Kidney stones

Kidney stones may be transplanted with the kidney or may be acquired. The incidence is less than 1% of transplants (46, 47). The stones manifest themselves by haematuria, infection or obstruction. Diagnosis may require non-injected CT scan. Some stones are eliminated spontaneously, but if stones do need to be removed, there are several options (48):

- The first step should be to try a double J-catheter or echo-guided percutaneous nephrostomy.
- Calyceal and smaller renal stones should be treated by extracorporeal shock wave lithotripsy (ESWL).
- Larger stones should be removed by percutaneous (49) or open nephrolithotomy.
- Ureterolithiasis should be treated by ESWL (50) or by ureteroscopy (51).

Recommendations
• Treat hyperparathyroidism in the recipient
• Use absorbable threads for the urinary anastomosis
• Treat urinary obstructions and infections
• Check calciuria

4.3.4 Renal artery stenosis

Renal artery stenosis has an incidence of 10% (range, 2-38%). It is suspected when existing arterial hypertension becomes refractory to medical treatment and/or there is an increase in serum creatinine without hydronephrosis (52, 53). It is diagnosed by Doppler sonography showing high velocity > 2m/s.

Treatment options include medical treatment and renal function follow-up, with interventional treatment indicated if the stenosis is > 70% (54). Transluminal dilatations, with or without stenting, give poorer results (70%) than surgery, but their simplicity makes them the first-line treatment for aligned and distal stenosis (33).

Open surgery is reserved for plication or anastomotic stenosis, failure of percutaneous dilatation and involves resection with direct implantation. Repair with the saphenous vein must be avoided.

Recommendations
• Use aortic patch from the donor
• Examine the artery intima, fix it or re-cut the artery when necessary
• Keep a long left renal vein, and lengthen the right one with the vena cava
• Avoid too tight anastomoses
• Use punch perforator when aortic patch is absent

4.3.5 Arteriovenous fistulae and pseudo aneurysms after renal biopsy

Arteriovenous fistulae are seen in 10% (range, 7-17%) of cases and are suggested by repeated haematuria (55, 56). Diagnosis is by Doppler ultrasound and is confirmed by MRI or by angiography. Angiography is also the first step in treatment. Fistulae may regress spontaneously (19), but when persistent haematuria or

when diameter > 15 mm, selective embolisation should be used. Pseudo aneurysms are often due to mycotic infection (57) and can be fatal.

Recommendation	GR
• Avoid very deep biopsy reaching the renal hilum	C

GR = grade of recommendation

4.3.6 Lymphocele

Lymphocele comprises 1-20% of complications. It occurs secondary to insufficient lymphostasis of the iliac vessels and/or of the transplant kidney. Obesity and the use of some immunosuppressant agents such as m-TOR inhibitors are associated with a higher risk oh lymphocele (58-60). Generally, it is asymptomatic, but there may be pain caused by ureter compression or infection. No treatment is necessary for mild lymphocele or if there is no compression of the iliac vessels or the transplant ureter. Otherwise, laparoscopic marsupialisation is the treatment of choice. Open surgery is indicated when laparoscopy (61) is not available or dangerous (62).

Recommendation	GR
• Strict lymphostasis should be maintained by clips or ligatures of the lymphatic vessels of the transplant and during dissection of the iliac vessels	C

GR = grade of recommendation

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4.5 Kidney transplantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- The technique used to implant transplant ureters in augmentations or conduits is the same as the method used with a patient's own ureter, e.g. following cystectomy for bladder cancer (Bricker, Wallace).
- In bladder augmentations or continent pouches, ureters are implanted by tunnel technique (Goodwin-Hohenfellner), or extravesically (favoured in most patients), e.g. using Lich Gregoir or Leadbetter methods (1-3).
- In ureterocystoplasty, it is feasible to perform uretero-ureterostomy with one of the patient's own ureters (1, 4).
- In patients with continent ileocoecal pouches with umbilical stoma or ileocystoplasties/ileal neobladders, transplant kidneys must be placed on the contralateral left side with the transplant ureters, crossing the abdomen subsigmoidally (2, 3, 5) (level of evidence: 3-4.)

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5. MATCHING OF DONORS AND RECIPIENTS

Recommendations	GR
• The ABO blood group and the HLA-A, -B, and -DR phenotypes should be determined for all candidates awaiting kidney transplantation	B
• To avoid hyper-acute rejection, a lymphocyte cross-match test must be performed before each kidney and combined kidney/pancreas transplantation	B

GR = grade of recommendation

5.1 Histocompatibility (HLA) matching

Histocompatibility (HLA) matching is still very important in kidney transplantation because transplant outcome correlates with the number of HLA mismatches (1, 2). HLA incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This leads to cellular and humoral graft rejection.

HLA antigens show remarkable polymorphism. Matching should concentrate on HLA antigens, which impact on rejection rates. The HLA-A, HLA-B, and HLA-DR phenotypes should be determined in all potential recipients and donors. Kidneys from deceased donors should preferentially be allocated to potential recipients with the lowest number of HLA mismatches. This is also true for living-donor transplantation, although HLA-compatibility is less important in living- than in deceased-donor kidney transplantation (3). In living-donor transplantation, other risk factors for graft rejection, e.g. cold ischaemia time, brain death and donor's age, can be minimised.

5.1.1 Practical aspects of HLA-testing

Laboratories that provide HLA-testing and cross-matching for a transplant centre must have a valid accreditation to ensure accuracy and reliability. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics. Other practical considerations include (4, 5):

- Obtain cells for HLA-typing from the recipient's peripheral blood using an appropriate anticoagulant, e.g. ammonium heparin, ethylene diamine tetra-acetic acid (EDTA) or acid-citrate-dextrose (ACD). Most HLA laboratories use 20 mL heparinised peripheral blood for serological HLA typing and 10 mL EDTA peripheral blood for molecular typing.
- Type donors using lymphocytes from lymph nodes, spleen, or peripheral blood.
- Use a comprehensive set of reagents capable of detecting all commonly occurring HLA antigens in the relevant ethnic group.
- For HLA-A and HLA-B specificities, serological or molecular typing is accepted. For HLA-DR, only molecular typing is accepted. For reporting HLA antigens, the latest WHO nomenclature should be used (6).
- Use family typing or DNA typing to detect possible homozygosity if the phenotype of a potential recipient shows fewer than six HLA-A, -B, -DR antigens.

5.2 Cross-matching

To avoid HAR, a cross-match test must be performed before each kidney and combined kidney/pancreas transplantation. Patients at risk are those who have HLA-specific allo-antibodies or have had an allo-immunising event, such as pregnancy, blood transfusion or a previous transplantation.

The cross-match test detects preformed allo-antibodies in the recipient's serum directed against lymphocytes of the potential donor. Routinely, a complement-dependent lymphocytotoxicity (CDC) assay is used. Cross-matches must be carried out using unseparated lymphocytes or T-enriched lymphocytes of the potential donor. B-cell cross-matches must be performed if required by the relevant transplantation programmes. T-lymphocytes express only HLA class I antigens. As B-lymphocytes express, besides HLA class I antigens also HLA class II antigens on their surface, a B-cell cross-match is considered to be more sensitive than a cross-match with T-lymphocytes. Spleen contains more B-lymphocytes than peripheral blood. A cross-match with unseparated lymphocytes from spleen is therefore more sensitive than a cross-match with unseparated lymphocytes from peripheral blood. A positive T-cell cross-match is generally a contraindication to transplantation. A positive B-cell cross-match result can occur for different reasons, including anti-HLA class I/II antibodies or allo-antibodies, immune complexes, therapy with anti-B-cell agents (rituximab, alemtuzumab), and non-HLA allo-antibodies (not shown yet). For a positive B-cell cross-match, individual decisions should be made based on the recipient's antibody status and immunological history. Sera obtained 14 days after a potentially sensitising event should be included in a final cross-match.

Be aware of false-positive cross-match results, especially in autoimmune diseases, which often exhibit clinically irrelevant IgM auto-antibodies. Inactivation of IgM antibodies by serum treatment with dithiothreitol (DTT) can minimise false-positive cross-match results. However, be aware that IgM-anti-HLA allo-antibodies are also DTT-sensitive. Anti-HLA allo-antibodies of the IgM isotype are rare and a positive cross-match result due to IgM-anti-HLA is currently considered as potentially relevant.

Flow cytometry cross-match may be used in presensitised recipients at high risk of antibody-mediated graft rejection. However, the great sensitivity of flow cytometric cross-match may exclude unnecessarily a high number of patients from transplantation (1, 7). An enzyme-linked immunosorbent assay (enzyme-linked immunosorbent assay, ELISA) cross-match test, which uses solid-phase technology to detect donor-specific anti-HLA antibodies, is being evaluated.

5.3 Pre-existing HLA-specific antibodies

Sera from potential organ recipients should be screened for HLA-specific antibodies every 3 months or as stipulated by the national and/or international organ exchange organisations.
Screening for HLA-specific antibodies should be carried out at 2 and 4 weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation.
The results of HLA-antibody testing in a recipient's serum are expressed as the percentage of panel reactive antibodies (%PRA) and as the HLA specificity against which these antibodies react. To detect antibodies to HLA class II antigens, a technique must be used that distinguishes them from antibodies to HLA class I antigens. In the standard CDC assay, the panel of lymphocytes used cover most of the common HLA-alleles in the donor population and should optimally contain at least 50 different HLA-typed cells.

As the assay is not sufficiently sensitive, clinically relevant anti-HLA class I and class II antibodies may go undetected in the traditional microlymphocytotoxicity assay (8). Non-complement fixing antibodies are not detected at all. More specific and sensitive solid-phase techniques have been developed, such as flow cytometry and ELISA, which use solubilised or recombinant HLA molecules instead of lymphocytes. Preformed non-HLA allo-antibodies may also influence graft outcome (9). Solid-phase assays are strictly HLA-specific and cannot detect non-HLA antibodies. It is not clear whether clinically relevant non-HLA antibodies are expressed on B-lymphocytes and can therefore be recognised by lymphocytotoxicity testing. No antibody screening methods can reliably detect all clinically relevant allo-antibodies, and a combination or alternate use of lymphocytotoxic and solid-phase antibody screening methods is therefore recommended (6).

Presensitised patients with high PRA have two major disadvantages:

- Due to an often positive cross-match, they generally wait longer for an organ than non-sensitised patients
- Overlooked antibodies or higher alloreactivity in the cross-match may adversely affect the graft outcome.

5.3.1 Eurotransplant Acceptable Mismatch (AM) programme

Special efforts, such as the acceptable mismatch (AM) programme of Eurotransplant, have achieved successful transplantation in highly sensitised patients (PRA ≥ 85%) (10). A careful analysis of HLA antibody specificities is carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. Patients accepted for the AM programme of Eurotransplant are given high priority during organ allocation if the donor cross-match test is negative.

5.4 ABO compatibility

Compatibility for ABO blood group antigens is of critical importance in kidney transplantation. Since blood group antigens can behave as strong transplant antigens (i.e. expression on renal vascular endothelium), incompatibility in the ABO antigen system between donor and recipient can cause early HAR and must be avoided. However, with the introduction of antibody elimination methods and anti-B cell agents, increasing numbers of centres are performing successful ABO-incompatible transplantations, even without splenectomy (11).

Despite an elevated risk of post-transplant haemolytic disease due to resting donor B-cells in the graft, the kidneys of potential donors with blood group O can theoretically be transplanted in A, B, or AB recipients. To avoid an increasing imbalance between demand and supply in deceased-donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys. In living-donor transplantation, ABO compatibility is as acceptable as ABO identity.

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6. IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION

6.1 Introduction

The principle underlying successful immunosuppression is 'the balance of survival'. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient's health. Increased understanding of immune rejection has led to the development of safe modern immunosuppressives (1), which suppress sensitised lymphocyte activity against a transplant. Immunosuppression is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.

In later post-operative stages, 'graft adaptation' occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) (2, 3) (level of evidence: 1b).

Non-specific side-effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections (1-3). All immunosuppressants also have dose-dependant specific side-effects. Current immunosuppressive protocols aim to reduce drug-specific side-effects using a synergistic regimen (4). A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs, so reducing side-effects, while still maintaining efficacy due to the synergistic effects of the immunosuppressants (level of evidence; 1b).

Current standard initial immunosuppression provides excellent efficacy with good tolerability (5, 6). It is given to most patients and consists of:

- CNIs (cyclosporine or tacrolimus)
- Mycophenolate (MMF or enteric-coated mycophenolate sodium, EC-MPS)
- Steroids (prednisolone or methylprednisolone)
- With or without induction therapy.

This multidrug regimen reflects today the standard of care for the majority of transplant recipients worldwide (5, 6) (level of evidence: 1b)

This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed (7). In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side-effects, lack of efficacy or protocol-driven requirements (3, 4, 6).

6.2 Primary immunosuppressive prophylaxis

6.2.1 Calcineurin inhibitors (CNIs)

Both cyclosporine and tacrolimus have significant side-effects that are hazardous to the graft and patient (1-3) (8, 9). Most importantly, both are nephrotoxic (10, 11) (level of evidence: 1a), and long-term use is a major cause of chronic allograft dysfunction, eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs (12).

6.2.1.1 Cyclosporine A

Cyclosporine A micro-emulsion (CsA-ME; Neoral) has a better pharmacokinetic profile and appears to be more acceptable to patients compared to the previous formulation (Sandimmune) (1, 6, 13, 14). More importantly, the area under the absorption curve is higher with CsA-ME than with Sandimmune, enabling a reduction in the dosage of cyclosporine without affecting efficacy (8). CsA-ME treatment is also associated with a reduced rejection rate 1 year post transplant (8) (level of evidence: 1b).

Although CsA-ME has proven efficacy and safety, it is a 'critical-dose' drug, so that any deviations from exposure can lead to severe toxicity or failure of efficacy (13, 14). The demonstration of bioequivalence in healthy volunteers according to standard criteria is not sufficient evidence to support treatment of all renal allograft recipients with generic formulations of cyclosporine. Until more data are available, the patient and physician prescibing generic cyclosporine formulations must be aware of potential differences in exposure, maximal drug concentration, variability and food effects (15, 16). Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one cyclosporine formulation to another (13, 14) (level of evidence: 2a).

Pharmaceutical companies and researchers are asked to provide sufficient data on key pharmacokinetic parameters in target populations, including de-novo transplanted patients. Drug agencies should institute more stringent criteria for 'critical dose' drugs requesting approval (level of evidence: 4).

Cyclosporine causes hypercholesterolaemia, hypertension, gum hypertrophy, constipation, hirsuitsm and acne (1-3, 8, 10) (level of evidence: 1a). Therapeutic drug monitoring is mandatory (17, 18) (level of evidence: 3) because of its narrow therapeutic window and the potential for drug-to-drug interaction. The drug level at 2 hours after intake (C2) may correlate better with exposure with retrospective studies suggesting a better correlation for C2 levels with outcome parameters (17, 18) (level of evidence: 3). However, no prospective comparative studies have been undertaken, and C2 levels alone may not adequately reflect cyclosporine exposure in the early post-transplant period (17, 18) (level of evidence: 2b). Furthermore, the determination of C2 levels may cause logistical problems. Most importantly, similar overall outcomes were achieved with conventional monitoring strategies. In summary, both cyclosporine-monitoring strategies are useful for assessing cyclosporine exposure. The additional measurement of a trough level in C2-monitored patients or of a C2 level in trough-level monitored patients may provide a more accurate assessment of drug exposure (18) (level of evidence: 4).

6.2.1.2 Tacrolimus

Tacrolimus is a more powerful immunosuppressive than cyclosporine, as indicated by its more potent prophylaxis of transplant rejection. However, its use is associated with diabetes, neurological side-effects (tremor, headache), hair loss, gastrointestinal side-effects (e.g. diarrhoea, nausea, vomiting) and hypomagnesemia (1-3, 8, 10) (level of evidence: 1a). In combination with a mycophenolate, it may also more often cause over-immunosuppression, namely polyoma nephritis (19) (level of evidence: 1b).

A new modified-release formulation (Advagraf), which allows once-daily dosing of tacrolimus (20, 21), has been approved in Europe, though not yet in the USA. Advagraf fulfils standard bioequivalence criteria, although it results in slightly lower exposure, lower peak levels and lower trough levels, which therefore require a higher dosage to maintain exposure (20-23) (level of evidence: 1b). Too low a level of exposure may be critical, especially early after transplantation.

Both tacrolimus formulations provide effective rejection prophylaxis and overall similar outcomes compared to cyclosporine (22) (level of evidence: 1b). Because of its narrow therapeutic window and the potential for drug-to-drug interaction, tacrolimus should be monitored using trough levels, which provide a reasonable estimate for exposure (20, 21) (level of evidence: 3).

6.2.1.3. Summary

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival (8) (level of evidence: 1a). Some analyses have shown that tacrolimus provided better rejection prophylaxis and was associated with slightly better graft survival, when censored for death in some analysis. Renal function was favourable for tacrolimus-treated patients, but did not reach statistical significance in most analyses. Several more recent trials have confirmed that rejection prophylaxis is better with tacrolimus (22, 24, 25), but failed to show any benefit with respect to patient and graft survival. Thus, in summary, both CNIs can be used for the effective prevention of acute rejection (level of evidence: 1a).

In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes,

polyoma nephropathy) conversion to the other CNI can be a successful strategy to reduce side effects (26, 27) (level of evidence: 1b). Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient (level of evidence: 4).

Despite their side-effects, CNIs have been a cornerstone of modern immunosuppresive regimens for more than 20 years because they have resulted in an exemplary improvement in kidney graft survival. This has led to success in pancreas, heart, liver, and lung transplantation (1) (level of evidence: 1a). Future protocols aim to minimise or even eliminate CNIs. However, until such strategies provide superior outcomes, CNIs remain the standard of care in the initial post-operative period (2, 3) (level of evidence: 1b). For severe CNI-related side-effects, CNI withdrawal, replacement or profound reduction may be needed (10) (evidence level 2b). Special attention should be paid to maintenance patients, which may need less CNIs than previously thought (26, 28) (level of evidence: 1b).

Recommendations	GR
• Rejection prophylaxis with CNIs represents current best practice pending publication of long-term results using newer agents	A
• The choice of CNI depends on the immunological risk, recipient characteristics, concomitant immunosuppression and socio-economic factors	A
• Blood-level monitoring of both cyclosporine and tacrolimus is mandatory to prevent under-immunosuppression (enhanced risk of rejection) and excessively high blood levels (resulting in a high risk of chronic side-effects, particularly nephrotoxicity)	A

GR = grade of recommendation

6.2.2 Mycophenolates

The mycophenolates, MMF and EC-MPS, are based on mycophenalic acid (MPA), which inhibits inosine monophosphate dehydrogenase. This is the rate-limiting step for the synthesis of guanosine monophosphate in the de-novo purine pathway. As the function and proliferation of lymphocytes is more dependent on de-novo purine nucleotide synthesis compared to other cell types, inosine monophosphate dehydrogenase (IMPDH) inhibitors may provide a more specific lymphocyte-targeted immunosuppression (1). Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause gastrointestinal side-effects particularly diarrhoea (29, 30). Both MPA formulations are equally effective with an almost identical safety profile (29) (level of evidence: 1b), though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking (31, 32) (level of evidence: 2a).

The co-administration of mycophenolate with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections (33) (level of evidence: 1b). A retrospective study Mycophenolate mofetil decreased the relative rate for chronic allograft rejection by 27% versus azathioprine, an effect independent of the reduction of acute cellular rejection in patients receiving MMF (33) (level of evidence: 3). Recent retrospective studies have suggested that MPA dose reductions are associated with inferior outcomes (31) (level of evidence: 3).

Other side-effects include the potential for over-immunosuppression, especially a higher incidence of CMV infections and severe CMV disease, and a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus (1-3) (level of evidence: 1b). Standard doses in combination with cyclosporine are MMF 1 g bid or EC-MPS 720 mg bid (level of evidence: 1b), although higher initial doses have been suggested, recently (34, 35) (level of evidence: 2b). MPA is not formally approved for use with tacrolimus, though this is the most frequently used drug combination in many countries worldwide (5). Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination (34, 35). Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine (34, 35) (level of evidence: 2a). Most transplant centres use the same starting dose compared to cyclosporine-treated patients (35) (level of evidence: 2b), however dose reductions are frequent, especially because of gastrointestinal side-effects (35). After 6-12 months, most patients are treated with a daily dose of MMF, 1000-1500 mg, or EC-MPS, 720-1080 mg (22, 24, 25). Due to the high incidence of side effects, some centers perform a protocol-driven MPA dose reduction in tacrolimus treated patients (34, 35) (level of evidence: 3).

Regular monitoring for polyoma is recommended in patients given MPA combined with tacrolimus (36, 37) (level of evidence: 3).

Due to a higher incidence of CMV disease with MPA, either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted (37-40) (level of evidence: 1a). CMV prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants, because prophylaxis recently has been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients (40) and leads to better long-term graft survival in kidney allograft recipients (38) (level of evidence: 1a).

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients (34, 35, 41-44) (level of evidence: 1b).

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients (45, 46) (level of evidence: 1a) or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function (2, 3, 28, 47) (level of evidence: 1b). Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first 3 years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies (47-49) (level of evidence: 1b). In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond 5 years' post-transplant and resulted in improved renal function (50, 51) (level of evidence: 1b). It is under investigation whether or not early CNI withdrawal under combination therapy of MPA, steroids and m-TOR inhibitors is safe and efficacious.

Recommendations	GR
• Mycophenolates are the current standard of care. The standard dose of MMF combined with cyclosporine is 1 g bid or EC-MPS 720 mg bid	A
• Combination therapy of mycophenolates with tacrolimus is not formally approved. Optimal mycophenolate dosing is not yet clear, as tacrolimus-treated patients develop higher MPA exposure compared to cyclosporine-treated patients. The standard starting dose of MMF combined with tacrolimus is MMF 1 g bid or EC-MPS 720 mg bid. This dosage, which is applied in most centres, is often reduced resulting in 30-50% lower doses at 1 year	A
• Mycophenolate drug monitoring cannot be recommended for all patients due to limited evidence supporting its benefit	A

GR = grade of recommendation

6.2.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprione, MPA reduced rejection rates significantly in prospective randomised trials (1, 5, 6, 28, 29) (level of evidence: 1b). Although a recent, large, prospective study found that azathioprine may give acceptable results in a low-risk population (52) (level of evidence: 1b), azathioprine is usually reserved for patients who cannot tolerate MPA (5, 6). When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters (53) (level of evidence: 1a).

Recommendations	GR
• Azathioprine may be used in a low-risk population as initial immunosuppression, especially for those intolerant to MPA formulations	A
• There is no firm evidence for the efficacy of azathiprine in combination therapy with CNIs and steroids	A

GR = grade of recommendation

6.2.4 Steroids

Steroids have a large number of side-effects (1-3, 45, 54), especially with long-term use. Most practitioners still consider prednisolone to be a fundamental adjunct to primary immunosuppression (5), even though successful prednisolone withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials (45, 46, 55, 56) (level of evidence: 1a). These trials suggest the risk of steroid withdrawal depends on the use of concomitant immunosuppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment peroid. (1-3, 45, 54, 57) (level of evidence: 3).

Recommendations	GR
• Initial steroid therapy remains the standard in perioperative and early posttransplamt period.	A
• There is increasing evidence that steroids may be safely stopped in most patients after 3-12 months on combination therapy with CNI and MPA	A
• Steroid-free long-term therapy is inherently associated with a reduction of steroid-induced side effects	A

GR = grade of recommendation

6.2.5 Inhibitors of the mammalian target of rapamycin (m-TOR)

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin (m-TOR) and suppress lymphocyte proliferation and differentiation. They inhibit both calcium-dependent and calcium-independent pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts and tumour cells (1-3, 57-60). m-TOR inhibitors are as effective as MPA when combined with CNIs in preventing rejection (57-60) (level of evidence: 1b).

6.2.5.1 Side-effects

m-TOR inhibitors exhibit dose-dependent bone marrow toxicity. Other potential side-effects include hyperlipidaemia, oedema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility (57-60) (level of evidence: 1b). When combined with CNIs, pneumocystis prophylaxis is mandated, e.g. low-dose cotrimoxazole (57-60) (level of evidence: 3). Most importantly, combination therapy with CNIs aggravate CNI-induced nephrotoxicity, although m-TOR inhibitors themself are non-nephrotoxic (57-60) (level of evidence: 1b). Several studies suggest less favourable outcomes for this combination, especially if CNIs are maintained at standard dosages (57-61) (level of evidence: 3). CNI dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on effcacy, due to the highly synergisitic potential of this combination therapy (57-60) (level of evidence: 1b).

6.2.5.2 Comparison of pharmacokinetics and licensed use

To date, no prospective comparative studies have been carried out on sirolimus and everolimus. Both m-TOR inhibitors have an almost identical side-effect profile and mainly differ in their pharmacokinetic properties (57-60). Sirolimus has a half-life of about 60 h, is given once a day and is licensed for prophylaxis of kidney recipients only. Everolimus has a half-life of about 24 h, is licensed for kidney and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine (57-60) (level of evidence: 1b) and can be given simultaneously with cyclosporine, while sirolimus should be given 4 h after cyclosporine (57-60). Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine (57-60) (level of evidence: 1b).

Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions (57-60) (level of evidence: 3).

6.2.5.3 Conversion from CNIs to m-TOR inhibitors

Despite an encouraging earlier metaanalysis (60), recent studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side-effect profile, particularly wound healing problems and lymphoceles (2, 3, 24, 57-60) (level of evidence: 1a). Other research suggests that m-TOR inhibitors can safely replace CNI at later stages, e.g. 3 months after transplantation, with improvements in renal function (2, 3, 57-60, 62) (level of evidence: 1a). However, especially early after transplantation, there is a slightly increased risk of rejection, which may be offset by the benefit of the non-nephrotoxic immunosuppression. Despite higher rejection rates, one study showed better long-term survival, better renal function and fewer malignancies under dual therapy with sirolimus and steroids compared to the more nephrotoxic therapy with cyclosporine, steroids and sirolimus. (2, 3, 57-60, 62) (level of evidence: 1b).

Proteinuria and poor renal function are associated with inferior outcomes. Conversion from CNI is not advisable in patients with proteinuria > 800 mg/day (57-60, 63, 64, 65) (level of evidence: 1b). A cautious and individual approach should be followed in patients with GFR < 30 mL/min (57-60, 63-65) (level of evidence: 3).

Due to an antiproliferative effect and a lower incidence of malignancy in sirolimus-treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy (57-60, 66) (level of evidence: 3). However, no controlled trials have reported better outcomes after conversion. To date, only a few data on long-term follow-up of m-TOR-treated patients have been reported. Emerging side-effects including proteinuria (66, 67) and infertility (68) warrant an individual and cautious approach (level of evidence: 3).

Recommendations	GR
• Acute rejection can be effectively prevented by m-TOR inhibitors, such as sirolimus and everolimus, in combination with CNIs. This combination regimen is associated with enhanced nephrotoxicity and inferior outcomes. CNI dosage must be significantly reduced to prevent aggravated nephrotoxicity	A
• Initial CNI-free combination therapy of m-TOR inhibitors with MPA and steroids is not sufficient to effectively prevent acute rejection compared to a standard regimen	A
• Use of m-TOR inhibitors is associated with impaired wound healing. Prophylactic surgical measures must be implemented if patients receive m-TOR inhibitors during the peri-operative period	A
• m-TOR inhibitors can safely replace CNIs beyond the early post-transplant period. They are a valid alternative to CNIs when there are severe CNI related side-effects, e.g. nephrotoxicity	A
• Blood levels of both sirolimus and everolimus must be measured at regular intervals	A

GR = grade of recommendation

6.2.6 T-cell depleting induction therapy

Prophylactic immunosuppression in many countries, particularly the USA, featured the emergence of 'induction' treatments, using biological T-cell depleting agents. These include anti-thymocyte globulin (ATG), OKT3 and more recently an anti-CD52 antibody (Campath1-H) after renal transplantation (1, 5).
Some centres use these agents to provide effective rejection prophylaxis while initiating CNIs after recovery of the graft from ischaemic injury, although evidence supporting this hypothesis is lacking (69, 70) (level of evidence: 1b). Graft rejection rates are initially lower with induction treatment (69, 70, 71); however, some studies suggest an increased rejection rate after cessation of lymphocyte depletion (70, 72). There is no evidence of better long-term graft survival in patients receiving induction therapy versus those who have not (70, 73-75) (level of evidence: 3). In contrast, it is well documented that induction therapies with T-cell depleting agents carry an increased risk of post-operative opportunistic infections and cancer, especially post-transplant lymphoproliferative disease (70, 73-75) (level of evidence: 3).

Recommendations	GR
• Potential life-threatening side-effects of T-cell depleting biological induction therapy include a higher incidence of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease	B
• Use of T-cell depleting antibodies has not been associated with improved outcomes in the overall population	B
• T-cell depleting antibodies should not be routinely used in a low-risk first-transplant recipient	B
• If such induction therapy is used, the increased risks of infection and cancer must be explained to the patient before staring therapy	B

GR = grade of recommendation

6.2.7 Interleukin-2 receptor antibodies

Two high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibodies (daclizumab and basiliximab) are approved for rejection prophylaxis following organ transplantation (1, 70, 76-78). These agents are given in a short course during the post-transplantation period, are safe, and have been shown in randomised controlled trials to reduce the prevalence of acute cellular rejection by approximately 40% (70, 78) (level of evidence: 1a). Both antibodies appear to be equally efficacious, though no formal comparative study was performed.

A meta-analysis has confirmed the efficacy, although no positive effect on patient or graft survival could be demonstrated (78) (level of evidence: 1a) although large retrospective cohort studies and a recent large prospective study suggest such a benefit (24, 70, 73, 75). The effect of these antibodies in combination with tacrolimus and/or mycophenolate was not investigated in the meta-analysis. Several recently published large controlled trials support the efficacy and safety of quadruple therapy with these agents (6, 22, 24, 25, 49, 55, 56, 70) (level of evidence: 1b). Interleukin-2 receptor antibodies may allow early steroid withdrawal (55, 56) (level of evidence: 1b), although higher rejection rates were described. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs, while maintaining excellent efficacy and renal function. (2, 3, 6 24, 47) (level of evidence: 1b).

Recommendations	GR
• Use of IL-2R antibodies for preventing rejection is efficacious and safe, and effectively reduces the rate of acute rejection, enabling CNI- and steroid sparing regimens	A

•	Formal evidence for improved patient and graft outcome is lacking, although recent large clinical trials suggest such a benefit	A

GR = grade of recommendation

6.2.8 References

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7. IMMUNOLOGICAL COMPLICATIONS

7.1 Introduction

Immunological rejection is a common cause of early and late transplant dysfunction (1, 2). There is great variation in the timing and severity of rejection episodes and how they respond to treatment (Table 19). There are several main types of immunological reaction (Table 20).

Table 19: Determining factors in rejection episodes and response to treatment (1-5)

• Degree of sensitisation to HLA, measured by the panel-reactive antibody (PRA) and specific anti-HLA antibodies
• Degree of HLA-mismatch, particularly in sensitised recipients (1)
• History of previous rejection episodes
• Previous transplantations, especially when graft loss has occurred due to acute rejection
• Non-compliance with immunosuppressive treatment
• Some virus infections, e.g. CMV

CMV = cytomegalovirus.

Table 20: Main types of rejection (1-7)

Hyper-acute rejection (HAR)
• Antibody-mediated rejection is caused by pre-formed anti-HLA or anti-AB (blood group) antibodies
• Now rare due to donor-recipient ABO matching and routine pre-transplant cross-matching between donor cells and recipient serum
Acute cellular rejection (ACR)
• Much more common than HAR, occurring in 10-40% of transplants
• Usually occurs from 5 days' post transplant
• Most likely within the first 3 months, though may occur after this time
• Usually responds well to steroid bolus treatment
Acute humoral rejection (AHR)
• Much less frequent than ACR, occurring in 5-20% of transplants
• Most likely within the first 3 months' post transplant
• Presence of certain histological features and/or positive C4d immunostaining and/or anti-HLA antibodies
• Worse prognosis than ACR because more difficult to treat
Chronic allograft rejection (CAR)
• Rare, slowly progressive, immunological process
• Certain non-specific histological features and/or anti-HLA antibodies
• Requires clear strong evidence for a solely chronic immunological process

The gold standard for the diagnosis of ACR, AHR and CAR is transplant biopsy (1, 2) (*see below*), which may demonstrate a mixed histological picture in many cases. The Banff criteria (6, 7) are uniform criteria applied to biopsy, which are updated regularly and are the basis for deciding prognosis and treatment (8) (level of evidence: 3).

The term 'IF/TA' replaces the previously used terms 'chronic allograft nephropathy'. This term was used to refer to chronic destruction of the graft associated with fibrosis and arteriosclerosis in renal biopsy and of uncertain aetiology. IF/TA is the common histological manifestation of some damage to the graft, where it is not possible to make a specific diagnosis of the underlying cause (6-9). IF/TA is probably the commonest histological feature in failed grafts and is present to some degree in the vast majority of grafts up to 10 years' post transplant (9).

'Chronic allograft dysfunction' is the term used to refer to the chronic deterioration of graft function without histological evidence (level of evidence: 4).

7.2 Hyper-acute rejection (HAR)

Hyper-acute rejection (HAR) is the most dramatic and destructive immunological attack on the graft (1-5). It results from circulating, complement-fixing IgG antibody, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium. It occurs in most ABO-incompatible grafts due to the presence of pre-existing IgM iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies (1-5) (level of evidence: 3).

With the development of the cross-match test, HAR has become an extremely uncommon complication. The complement-dependent cytotoxicity test (CDC) is now universally employed in all transplant centres. Recently, newer techniques have been developed, allowing a more sensitive detection of specific anti-HLA antibodies (4, 5) (see Chapter 5). However, validation of these techniques is ongoing. If such diagnostic tests demonstrate the possibility of specific anti-HLA antibodies in the presence of a negative CDC cross-match, an individual decision has to be made whether to transplant or not (level of evidence: 4).

Hyper-acute rejection is a rare complication usually seen at the time of surgery. Within minutes or hours of vascularisation, the kidney becomes mottled and then dark and flabby. Histology reveals generalised infarction of the graft (4). Delayed HAR may occur within a week of the transplant, and may be recognised by acute anuria, fever and a swollen graft. Hyper-acute rejection is treated by graft nephrectomy.

7.2.1 Prevention

Hyper-acute rejection can be prevented by the avoidance of an ABO-incompatible renal transplant and by performing a regular CDC cross-match before transplantation (level of evidence: 3). All patients registered for renal transplantation should have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions (4, 5, 10) (level of evidence: 3). Highly sensitised patients (> 50% PRA) should be considered for prioritisation in a points-based matching algorithm (10) (level of evidence: 3).

In a national kidney-sharing programme, identification of the specificity of anti-HLA antibodies in highly sensitised patients and cross-matching allows the detection of acceptable and unacceptable antigens present in the donor (10). This information can be highlighted with the patient's details on the transplant registry database, so preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity (10) (level of evidence: 3).

Recommendations	GR
• All recipients and donors must be tested for blood group antigens and blood group incompatibility must be avoided, except intentional living-donor ABO-incompatible transplantation	B
• All centres practising renal transplantation should have access to elective serological profiling of all potential, and actual, waiting-list recipients to define the percentage and specificity of PRA and their isotypes, IgG or IgM	B
• The laboratory service should provide a 24-h donor-recipient cross-matching service to be able to quickly inform a surgeon of the CDC cross-match result before a deceased donor renal transplant (within 5 h)	B

PRA = panel-reactive antibody; CDC = complement-dependent cytotoxicity (testing);
GR = grade of recommendation

7.3 Acute allograft rejection

Acute allograft rejection can be classified into either T-cell mediated (acute cellular rejection, ACR) or antibody-mediated (acute humoral rejection, AHR) according to the most recent Banff criteria (1-7). Tubulo-interstitial infiltrate of T-cells, macrophages, and to a lesser extent, neutrophils invading the tubular epithelium is a hallmark of T-cell mediated ACR.

Humoral rejection commonly accompanies ACR and causes the same clinical signs. As in ACR, the diagnosis of AHR becomes apparent on renal allograft biopsy. It can be categorised into capillary or arterial antibody-mediated rejection. During post-operative humoral rejection, antibodies are formed against donor antigen on the endothelium. In 20-25% of cases, these antibodies may be detected in the serum during rejection (4, 5). Acute humoral rejection is under-diagnosed (11, 12). On biopsy, the appearance may be of oedema and

haemorrhage with focal necrosis. The C4d fraction of complement in renal biopsy is required for diagnosis according to the current Banff criteria (6, 7, 11, 12). Not surprisingly, the prognosis is poorer than when ACR occurs alone (4, 5, 11, 12) (level of evidence: 3).

Because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis or CNI nephrotoxicity), a biopsy is necessary to correctly diagnose and treat the patient (1-6) (level of evidence: 3). If possible, all rejections must be verified by renal biopsy and graded according to the most recent Banff criteria, except when contraindications for a renal biopsy are present (6-8) (level of evidence: 3). Renal transplant biopsy should be conducted preferably under ultrasound control, using an automated needle biopsy system (e.g. tru-cut, biopsy gun) (13) (level of evidence: 3).

Recommendations	GR
• Renal transplant practitioners must be continuously aware of the possibility of acute rejection, particularly during the first 6 months after renal transplant	B
• During hospitalisation, regular blood and urine samples should be taken for renal and haematological studies in addition to regular ultrasound examinations	B
• Rejection should be strongly suspected in any patient who suffers fever, graft tenderness, or reduced urine output. In case of suspected acute rejection, other potential causes of graft dysfunction need to be ruled out immediately	B
• All patients with suspected acute rejection episodes should undergo renal biopsy, which should be graded according to the most recent Banff criteria. Only if contraindications to r enal biopsy are present, can 'blind' steroid bolus therapy be initiated. Steroid treatment for rejection may start before biopsy is performed	B
• There should be routine access to ultrasound-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a clear-cut diagnosis of rejection or other type of allograft dysfunction	B
• Staff and facilities on renal transplant units should be sufficiently equipped to admit a patient with acute rejection immediately to allow rapid diagnosis and treatment	B
• Patients who suffer ACR should be tested as soon as possible for anti-HLA IgG antibodies reactive with the graft	B

GR = grade of recommendation

7.3.1 Treatment of T-cell mediated acute rejection

As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience than on clinical evidence (1-4, 14). Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for 3 days (1-4) (level of evidence: 3). Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another 3-day course of pulsed methylprednisolone therapy (1-4) (level of evidence: 3). In addition, baseline immunosuppression should be re-evaluated to ensure adequate drug exposure (1-4) (level of evidence: 3).

In severe rejection, a conversion from cyclosporine to tacrolimus should be considered (1-4) (level of evidence: 3). T-cell depleting biological agents, such as ALG or anti-CD3 monoclonal antibody (OKT3), may be considered in severe steroid-refractory cases (1-4, 14) (level of evidence: 1a). If biological agents are used, other immunological suppression should be reduced or stopped and daily T-cell monitoring should be done to minimise the dose of the biological agent (15, 16) (level of evidence: 4). Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately (level of evidence: 4).

Recommendations	GR
• Treatment with steroid bolus therapy is recommended	B
• In severe or steroid-resistant rejection, consider intensified immunosuppression, including high-dose steroid treatment, conversion to tacrolimus, and T-cell depleting agents	B

GR = grade of recommendation

7.3.2 Treatment of acute humoral rejection (AHR)

Acute humoral rejection is treated in a similar way as T-cell mediated rejection (4, 17) (level of evidence: 3). Treatment relies on retrospective studies and empirical treatment guidelines. Treatment with a steroid bolus (at least 3 days of 500 mg/day) and conversion to tacrolimus therapy with trough levels > 10 ng/mL are common (4, 17) (level of evidence: 3). Although T-cell depleting agents appear to have limited value, there are several

retrospective case series and a small prospective trial in children and adolescents describing the successful use of the anti-CD20 antibody, rituximab (4, 17, 18) (level of evidence: 1b). However, no further prospective trials have been published and neither the dose, side-effects nor efficacy parameters have been evaluated in a larger cohort with adequate follow-up. Most centres also try to remove antibodies using plasmapheresis or immunoadsorption columns. Retrospective and prospective case series clearly suggest efficacy (4, 17, 19) (level of evidence: 1b), although details of the procedures vary widely.

Some centres advocate intravenous immunoglobulin (20), which may modulate and/or suppress antibody production (4, 17, 20) (level of evidence: 3). Dosages vary widely from 0.2-2.0 g/kg bodyweight. No comparative studies have been published. Several regimens have proven efficacious in AHR. However, the lack of firm evidence does not permit evidence-based recommendations for treatment, except for a beneficial effect of early antibody removal.

Recommendations	GR
• Treatment of AHR should include early antibody elimination	B
• In addition, steroid bolus therapy, conversion to tacrolimus, T-cell depleting agents and intravenous immunoglobulin treatment are used frequently	B
• Anti-CD20 (rituximab) may be efficacious. However, firm evidence on efficacy and side-effects are lacking	B

GR = grade of recommendation

7.4 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy (IF/TA)

Many patients lose their grafts due to chronic allograft dysfunction (9). Histology will usually reveal a chronic process of IF/TA. An unknown, but rather small number of these patients will have 'true' immunological CAR (1, 2). IF/TA takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum creatinine level over months (9). It is likely that IF/TA is more common in patients who have had early attacks of ACR, which is a good reason for preventing acute cellular rejection. The main differential diagnoses are chronic nephrotoxicity, which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney (9). Histological features on biopsy are fibrosis, cortical atrophy, concentric intimal fibroplasia of larger arteries with capillary dilatation, arteriolar hyalinosis, and thickened split basement membranes. (Level of evidence: 3).

7.4.1 Diagnosis and treatment

Diagnosis is by renal biopsy (5, 6). In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen (22-24) (level of evidence: level 1a). Conversion to m-TOR inhibitors is safe. Favourable outcomes have been observed without significant proteinuria (< 800 mg/day) (24, 25) (level of evidence: 1a). Alternatively, successful conversion to a MPA-based regimen has been described, especially in patients beyond the first 3 years' post transplant (22, 23) level of evidence: 1b). If there is intolerance to m-TOR inhibitors or MPA, conversion to an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance (26) (level of evidence: 1a). If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA (21, 27) (level of evidence: 1b). In patients with proteinuria, intervention with an ACE inhibitor or angiotensin II receptor blocker (28) may slow down renal decompensation (level of evidence: 3). Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis and bone disease (29-34) (level of evidence: 3). However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

Recommendations	GR
• During the years of follow-up after renal transplantation, regularly monitor serum creatinine, creatinine clearance, blood pressure and urinary protein excretion • Changes in these parameters over time should trigger hospital admission for renal biopsy and further diagnostic work-up including a search for infectious causes and anti-HLA antibodies. An ultrasound of the graft should rule out obstruction and renal artery stenosis	A
• If a specific cause for deteriorating renal function can be identified, appropriate treatment should be instituted	A
• If unspecific IF/TA is confirmed, begin appropriate medical treatment (e.g. control of hypertension, proteinuria)	A

•	Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease) and cardiovascular risk factors (e.g. hyperlipidaemia, diabetes)	
•	In patients with IF/TA under current CNI therapy and/or with histological signs suggestive for CNI toxicity (e.g. arteriolar hyalinosis, striped fibrosis) without significant proteinuria (< 800 mg/day), conversion to an m-TOR inhibitor or substantial CNI reduction under MPA protection may be indicated. In chronic maintenance patients beyond 5 years, post-transplant CNI withdrawal under MPA and steroids is another safe option	A

GR = grade of recommendation

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8. MALIGNANCY

There are three situations in which malignancy occurs in kidney transplant recipients:
1. Transmitted malignancy by the donor
2. Known or latent prior malignancy in the recipients
3. 'De-novo' malignancies developed in the recipient after transplantation.

8.1 Transmission of a donor neoplasia to the recipient

The risk of a donor disease transmission is estimated at 0.2% (1) with increased use of older donors and marginal kidneys. Donors can be divided into three groups according to the risk of transmission of cancer:
- Donors without cancer
- Donors with a per-operative diagnosis of cancer
- Donors with a history of cancer.

However, even in the first situation, there remains a very small risk that donors may carry an infraclinical tumour, particularly of the prostate (2).

Pre-operative suspicion of cancer was reported in 337 (4.4%) out of 7608 donors (3). Among them, there were 131 donors suitable for donation, who donated a total of 241 organs without any donor-related tumour transmission to the recipients. In 1069 donors with a history of cancer and no tumour transmission, the most common cancers were non-melanoma skin cancer (31%), central nervous system (CNS) tumours (25%), and uterine and cervical cancers (13%) (4). Melanoma and choriocarcinoma are the most aggressive donor-transmitted malignancies (5).

Individuals with active cancer or a history of metastatic cancer or who have had cancers with a high risk of recurrence (e.g. medulloblastoma and glioblastoma multiform) should not be donors (6). Occasionally, brain metastasis may masquerade as a primary brain tumour or cerebral haemorrhage and must be excluded as it is a contraindication for donation.

However, a prior history of neoplasia is no longer an absolute contraindication for organ donation. Non-melanoma low-grade skin cancer and selected CNS tumours that have not undergone surgical manipulation may also be acceptable. The following tumours are not contraindications to donation:
- Basal cell carcinoma
- Non-metastatic spinocellular carcinoma of the skin
- Cervical carcinoma *in situ*

- Carcinoma in situ of the vocal cords.

There is no consensus on donors with transitional cell carcinoma of the bladder at the Ta G1 (TNM) stage. Screening for prostate cancer is different from country to country and is suggested only when there are reasons for such a test.

Donors affected by certain low-grade (grades 1 and 2) brain tumours (Table 21) are suitable for kidney donation. Individuals affected by brain tumours of any grade who have undergone ventriculo-peritoneal shunting must be excluded because of the high risk of systemic dissemination of tumour cells through the shunt (level of evidence: 3).

Table 21: Low-grade brain tumours that do not exclude organ donation

• Low-grade astrocytoma
• Pituitary adenomas
• Epidermoid cysts
• Colloid cysts of the third ventricle
• Pilocytic astrocytoma, ependymoma
• Low-grade oligodendroglioma (Schmidt A and B)
• Choroid plexus papilloma
• Ganglionic cell tumour (ganglioma, gangliocytoma)
• Benign meningioma
• Craniopharyngioma
• Haemangioblastoma (not associated with Von Hippel Lindau syndrome)
• Acoustic Schwannoma
• Pineocytoma
• Well-differentiated teratoma

When a kidney has been transplanted from a donor with a post-transplant diagnosis of cancer, graft nephrectomy and suspension of immunosuppression are not always necessary. The risks and benefits should be discussed with the recipient.

Due to a low risk of recurrence, kidneys with small renal cell carcinoma (RCC) can be considered for local excision and transplant after the recipient has given informed consent. The risk of RCC transmission to the contralateral kidney and/or to other organs is even lower; again, the patient's informed consent is necessary (level of evidence: 4).

Recommendations	GR
• Donors with active cancer or history of metastatic cancer and cancers with a high risk of recurrence should not be considered as possible donors	C
• A prior history of neoplasia is no longer an absolute contraindication for organ donation	C

GR = grade of recommendation

8.2 Prior malignancy in the recipient

Any active tumour in the recipient is an absolute contraindication for kidney transplantation because of the risk of dissemination and fatal outcome. However, a previous history of cancer does not automatically exclude transplantation. It can be difficult to decide who should be considered as suitable for transplantation and particularly 'when'. So far, clinical decision has been mainly based on the Cincinnati Registry, which essentially considers the type of tumour and the delay between its treatment and kidney transplantation. However, a better approach would be based on type of tumour, TNM stages, and the risk of recurrence after treatment.

For most tumours, the waiting time for transplantation is 2 years on the Registry. However, a 2- year waiting period would eliminate only 13% of colorectal recurrences, 19% of breast cancer recurrences, and 40% of prostatic cancer recurrences (7, 8). In contrast, a 5-year waiting period would eliminate most recurrences, but this is not practical in the elderly (9) and unnecessary for most tumours. There is therefore not enough evidence to support a fixed waiting period before transplantation.

Recipients who have tumours with a low recurrence rate can be considered for immediate transplantation after successful treatment of the tumour (e.g. incidental RCC, non-melanoma skin cancer and *in-situ* uterine/ cervical cancer). In the remaining cases, because of the risk of dormant metastases, the waiting period should

be individualised according to the type and TNM stage and grade of the tumour, age and recipient's general condition. Patients on the waiting list and after transplantation must be evaluated regularly to detect recurrence (level of evidence: 4).

Modification of immunosuppression may be considered in these patients following a recent report that the use of m-TOR inhibitors is associated with a reduced incidence of malignancy (10), as is similarly a reduction in immunosuppressive therapy.

Recommendations	GR
• Any active tumour in the recipient is an absolute contraindication for kidney transplantation because of the risk of dissemination and fatal outcome	C
• The waiting period before transplant in recipients with a history of malignancy depends on the type, TNM stage and grade of the tumour, and recipient's age and general health	C
• Recipients with tumours that have a low recurrence rate can be considered for immediate transplantation after successful treatment	C
• Close follow-up is mandatory particularly after transplantation	C

GR = grade of recommendation

Patients with ESRD on the waiting list for kidney transplantation will be ageing, and thus carry a higher, potential risk of latent neoplasia being activated following kidney transplantation. Candidates for kidney transplantation, particularly > 50 years old, should be screened for the presence of a pre-existing cancer (Table 22).

Table 22: Screening of potential recipients for malignancy

• Exhaustive history and physical examination, including a dermatological examination
• Gynaecological examination: vaginal cytology and colposcopy, regardless of age
• Mammography in women over 40 years old or with a family history of breast cancer
• Prostate examination: prostate-specific antigen (PSA) levels and digital rectal examination (DRE) in men aged over 50 years.
• Faecal occult blood testing or colonoscopy according to current guidelines
• Chest X-ray
• Abdominal ultrasound to exclude renal cell carcinoma or other abdominal tumour

8.3 'De-novo' tumours in the recipient

The risk of cancer after kidney transplantation is several times higher than in the general population (11, 12). Post-transplantation cancer is one of the most common long-term causes of death; with up to 35% of heart transplant recipients dying of cancer (13). Most malignancy affects the skin (40%) or the lymphatic system (11%). Several factors contribute to the high prevalence of cancers in transplant recipients (Table 23). Annual screening is mandatory to detect a new cancer or co-morbidity.

Table 23: Factors increasing risk of de-novo tumour in recipient

• Sun exposure: skin cancer
• Analgesic abuse: urothelial cancer
• Acquired multicystic renal disease: renal cancer
• Immunosuppressants, e.g. CNIs and lymphocyte-depleting antibodies
• Viral infections, e.g. EBV, herpes 8 virus, human papillomavirus, HBV, HCV, HEV

8.3.1 Skin cancer and Kaposi's sarcoma

The risk of skin cancer increases with age (> 50 years) (14), cyclosporine (10) and duration of immunosuppression. Its incidence rises with time to 5% at 5 years, 16% at 10 years and 52% at 20 years' post transplant (15). Skin cancer represents 40-60% of post-transplantation tumours, with up to 50% of all skin cancers being squamous cell. The male-to-female ratio is 4.8 to 1.3 (16). It is closely linked to sun and ultraviolet exposure, the presence of HLA-B27 antigen and the degree of immunosuppression. Skin cancer often recurs, particularly in heart and kidney recipients (17). An annual dermatological examination and use of total sun block are recommended (18, 19) (level of evidence: 2a).

The prevalence of Kaposi's sarcoma ranges from 0.5% to 4%, depending on the country (20). It is associated with HHV8 positive serology. Screening for HHV8 in high-risk patients (Mediterranean countries) and

prophylactic measures may be considered (21) (level of evidence: 3). The use of m-TOR inhibitors may be preferrable over CNIs, which seem to promote the appearance of Kaposi´s sarcoma (19) (level of evidence: 3)

Recommendations	GR
• Oral and written information on the risk of skin cancer and protective measures should be given	C
• Dermatological examination before, and at least annually after, transplantation is mandatory	C
• The use of m-TOR inhibitors instead of CNIs is advised in patients with Kaposi´s sarcoma or a history of Kaposi´s sarcoma	C

GR = grade of recommendation

8.3.2 Lymphatic disease

Post-transplantation lymphoproliferative disease (PTLD) is a life-threatening complication because of extra-nodal dissemination and a poor outcome (12, 22). The incidence (1-5%) has increased since the introduction of cyclosporine (23) and the induction regimen by ALG and OKT3 with a SIR (standardized incidence ratio) between 9 and 29 (24). The disease usually occurs within the first year after transplantation and is characterised by non-Hodgkin's lymphomas and EBV-infected B-lymphocytes. Treatment involves reduction or even suspension of immunosuppressive therapy, with a remission rate of 50-68%. Anti-CD20 antibody therapy, with or without chemotherapy, and antiviral drugs (acyclovir, ganciclovir) may be helpful (25, 26) (level of evidence: 3).

Recommendations	GR
• Use of induction therapy with T-cell depleting agents should be restricted whenever possible	C
• Clinical examination every 3 months during the first post-transplant year is advised for young recipients and for patients who have received T-cell depleting agents	C

GR = grade of recommendation

8.3.3 Gynaecological cancers

Cervical cancer is 3 to 16 times more common in transplanted females compared to the general population. In 70% of cases, it will be *in-situ* carcinoma or cervical intraepithelial neoplasia (CIN).

Cervical cancer appears to be arising from infection of the cervix with sexually transmitted oncogenic strains of human papillomavirus (HPV). Increased risk of cervical cancer in transplant recipients is due to re-activation of latent HPV in the immunosuppressed recipient. The prevalence of HPV in the cervix of transplanted females is almost 45%, though this figure is currently decreasing, as is also CIN prevalence (27). Data on successful HPV immunization are not available, but young female transplant recipients may benefit from HPV immunization.

Annual colposcopy and cytology are required. Mammography and gynaecological ultrasound should be periodically performed, although formal evidence for this preventive strategy is lacking (28) (level of evidence 4).

8.3.4 Prostate cancer

The prevalence of clinical prostatic adenocarcinoma in the male transplanted population is 0.3% to 1.8%. Prevalence increases with the age of the recipient and can reach 5.8% if PSA screening is performed in all males. All recipients over 50 years old should have an annual PSA test and DRE. Prostate serum antigen levels are not modified by kidney transplantation and most prostate cancers detected in transplanted patients are clinically localised (84%) at diagnosis (29) (level of evidence: 4).

8.3.5 Bowel cancer

The association of colon cancer with kidney transplantation is much more controversial than for other cancers, even though an increased risk factor of 2.6 has been reported at 10 years' post transplant.However, it is difficult to advise on the most appropriate method of follow-up and its frequency. An annual faecal blood test is acceptable and cost-effective, but not performed routinely worldwide. Colonoscopy every 5 years is also acceptable in the absence of other factors implying a high risk of colon cancer, despite the absence of data on screening in this population. A risk factor is the re-activation of CMV and EBV infections (28) (level of evidence: 4).

8.3.6 Urothelial tumours

The incidence of urothelial tumours is three times higher than in the general population (29). Tumours are usually transitional cell neoplasia, though the incidences of bladder adenocarcinoma and nephrogenic adenoma have both increased. Urinary cytology is routinely performed in patients with microhaematuria,

analgesic nephropathy, or a prior history of urothelial cancer, despite its poor sensitivity of 30%. Recipients with gross haematuria should undergo a detailed study of the whole urinary system, bladder, ureters and kidneys.

8.3.7 Renal tumours

Renal cell carcinoma usually occurs in the patient's own kidneys, but can also present in the graft. The prevalence ranges between 0.5% and 3.9%, which is 10 to 100 times greter than in the general population (29). The main risk factor is the presence of acquired chronic kidney disease (ACKD). Other risk factors include previous history of RCC, Von Hippel Landau disease and (perhaps) polycystic kidneys. The main histological patterns are RCC and tubulopapillary carcinoma (30).

Annual ultrasound of the patient's native kidneys and the graft is recommended (28, 29) (level of evidence: 4). Any renal solid tumour should be treated with retroperitoneoscopic or laparoscopic nephrectomy (level of evidence: 4).

8.3.8 Chest X-ray

An annual chest X-ray is recommended in order to detect lung cancer and cardiothorarcic abnormalities (28) (level of evidence: 4).

Recommendations grade B/C		GR
•	The risk of cancer is several times greater in transplanted patients than in the general population and is the main concern of the medical team in the long-term follow-up of all organ recipients	B/C
•	Screening should be carried out annually for cancers of the skin, lymphatic system and native kidneys. For all other organs, screening should be the same as in the general population	B/C

GR = grade of recommendation

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9. ANNUAL SCREENING

The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population (1, 2). Cancer is a cause of significant morbidity and mortality in the transplanted population (1). Cardiovascular disease is the most frequent cause of death in renal allograft recipients (2, 3) (level of evidence: 3).

9.1 Recommendations for annual screening

The following recommendations can be made for annual screening of a transplant recipient. They include:

- Lifelong regular post-transplant follow-up by an experienced and trained transplant specialist is strongly recommended at least every 6-12 months
- More frequent follow-up visits (e.g. every 4-8 weeks) for renal function and immunosuppression and side-effects by a physician
- Annual screening should include a dermatological examination, tumour screening (including a nodal examination, faecal occult screening, chest X-ray, gynaecological and urological examination), and an abdominal ultrasound, including ultrasound of the native and transplanted kidney)
- Special attention during post-transplant care should also focus on proteinuria, recurrence of original disease
- posttransplant care should aim to detect cardiac disease and cardiovascular risk factors. Cardiac exam and cardiac history should be taken, and if appropriate further diagnostic tests should be prompted to exclude the progression of cardiac disease
- Blood pressure, blood glucose and blood lipids should be determined at appropriate intervals, and adequate measures to control this risk factors should be instituted.
- The physician should also focus on the adequate prophylaxis, detetction and treatment of concomitant diseases (e.g. bone disease, anemia) and infections.

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10. GRAFT AND PATIENT SURVIVAL

Recommendations	LE	GR
• Graft survival following unselected kidney transplantation should be at least 85% after 1 year and 70% after 5 years (1,2) (Figure 1)	3	B
• Patient survival following unselected kidney transplantation should be at least 90% after 1 year and 85% after 5 years (1,2) (Figure 2)	3	B

LE = level of evidence; GR = grade of recommendation

Figure 1: Improvement of graft survival following kidney transplantation during the last two decades

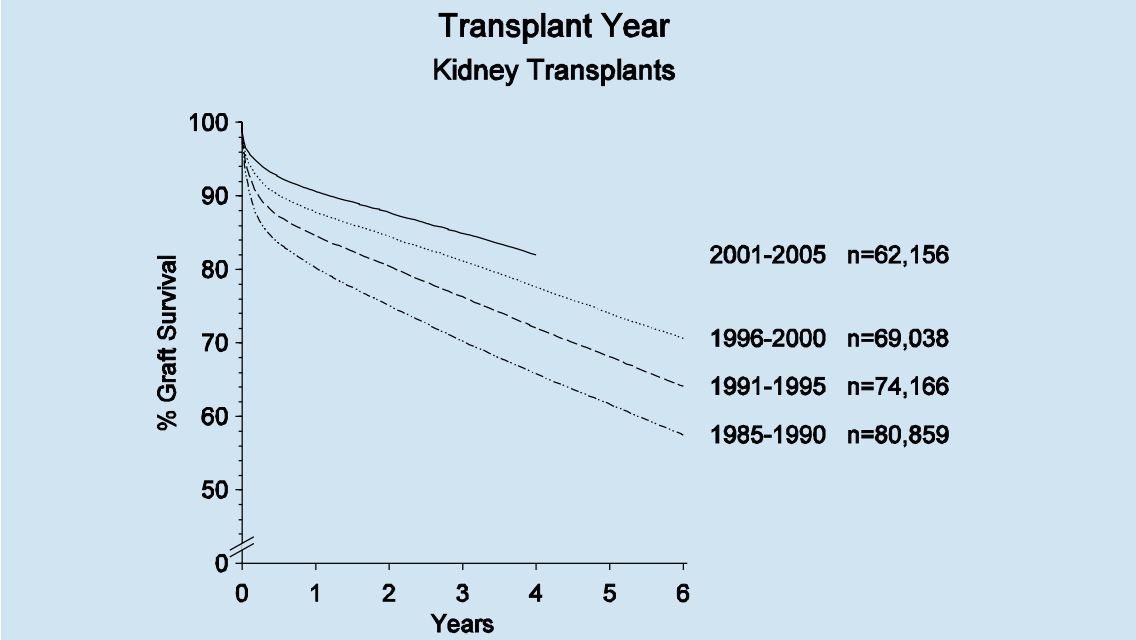

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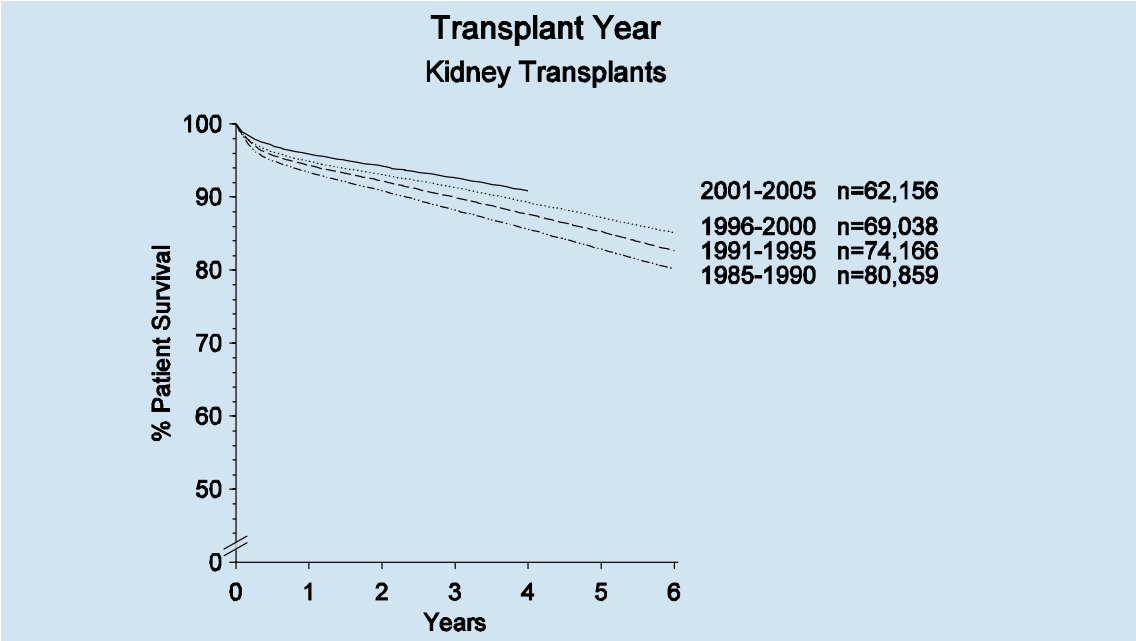
Figure 2: Improvement of patient survival following kidney transplantation during the last two decades



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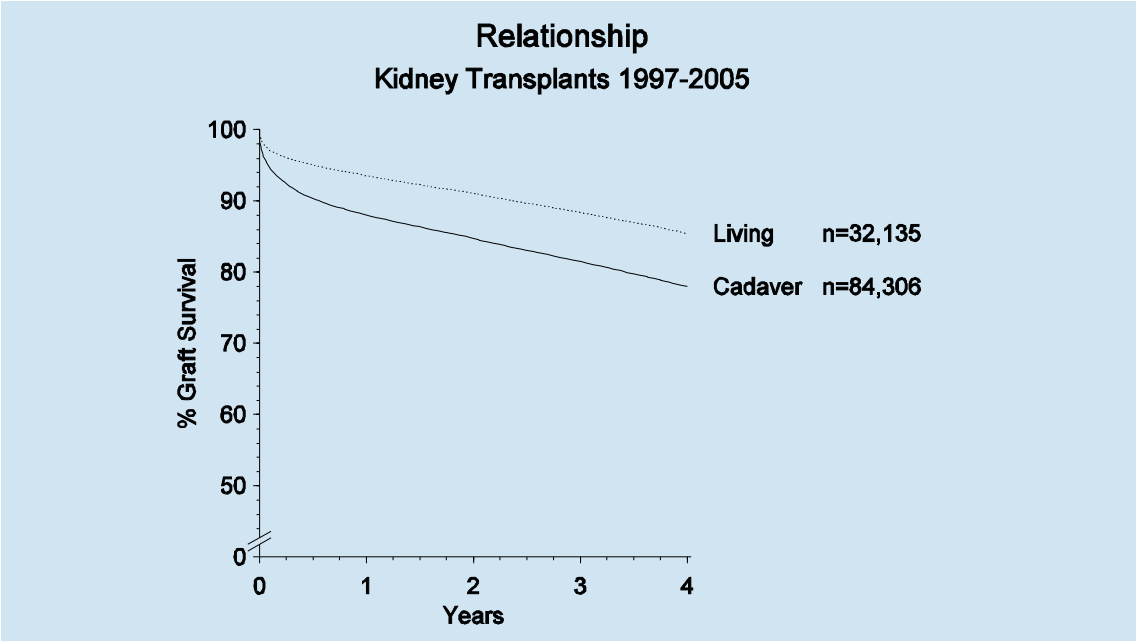
This general outcome following kidney transplantation depends on several criteria that are discussed below:

10.1 Deceased and living donors

10.1.1 Graft survival

Graft survival after living-donor kidney transplantation is generally better than after deceased-donor kidney transplantation (Figure 3). A better selection of donors, absence of brain death and a shorter cold ischaemia time are the most likely explanations.

Figure 3: Graft survival following deceased- and living-donor kidney transplantation



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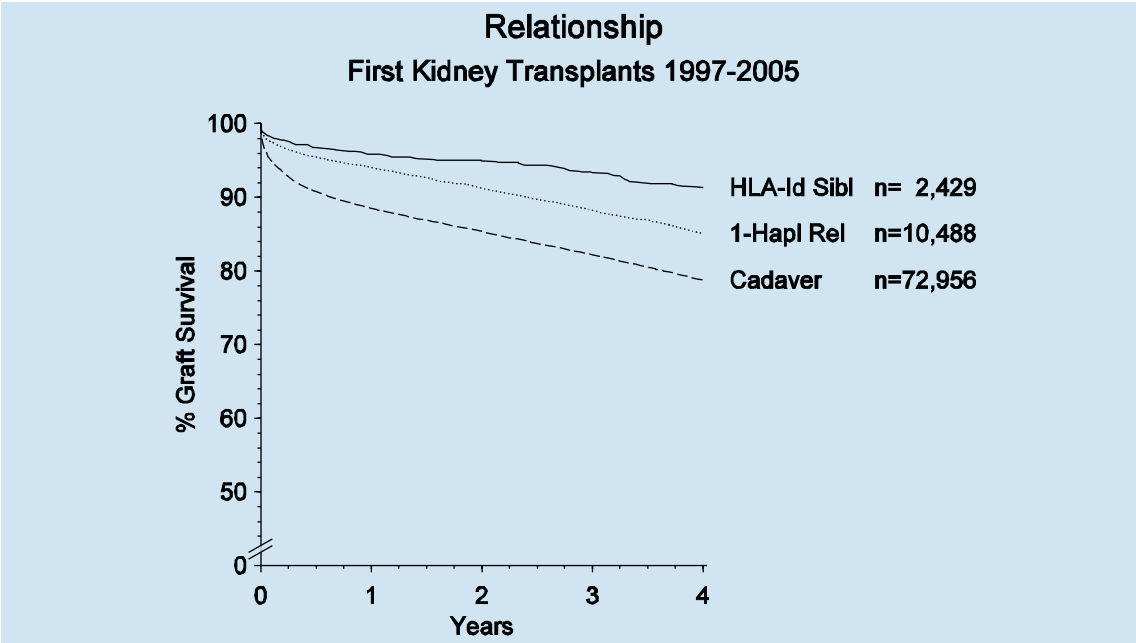
The 1-year graft survival of living-donor kidney is in mean 97% for HLA-identical siblings and 95% for 1-haplotype-identical related donors compared to 88% for deceased-donor kidneys (Figure 4). The 3-year graft survival of living-donor kidney is in mean 95% for HLA-identical siblings and 90% for 1-haplotype-identical related donors compared to 83% for deceased- donor kidneys (Figure 4).

Figure 4: Graft survival following deceased- and living-donor kidney transplantation.



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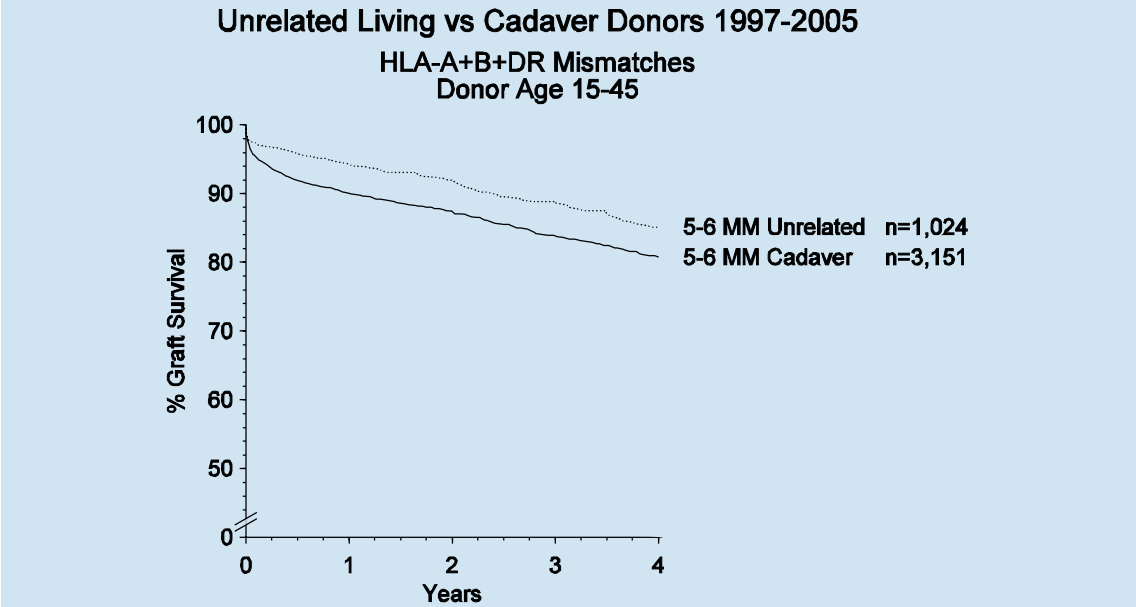
Excellent graft outcomes have been reported in unrelated living-donor transplantation, even if the donor-recipient pairs were poorly HLA-matched (3). CTS data show that poorly matched kidneys from unrelated living donors demonstrate a much better outcome than poorly matched kidneys from deceased donors. However, this difference almost disappears in donors aged between 15 and 45 years old (Figure 5). This suggests that a good outcome in unrelated living-donor transplantation may mainly be due to optimal selection of donors and absence of brain death.

Figure 5: Graft survival in poorly HLA-matched deceased-donor and unrelated living-donor kidney transplantation



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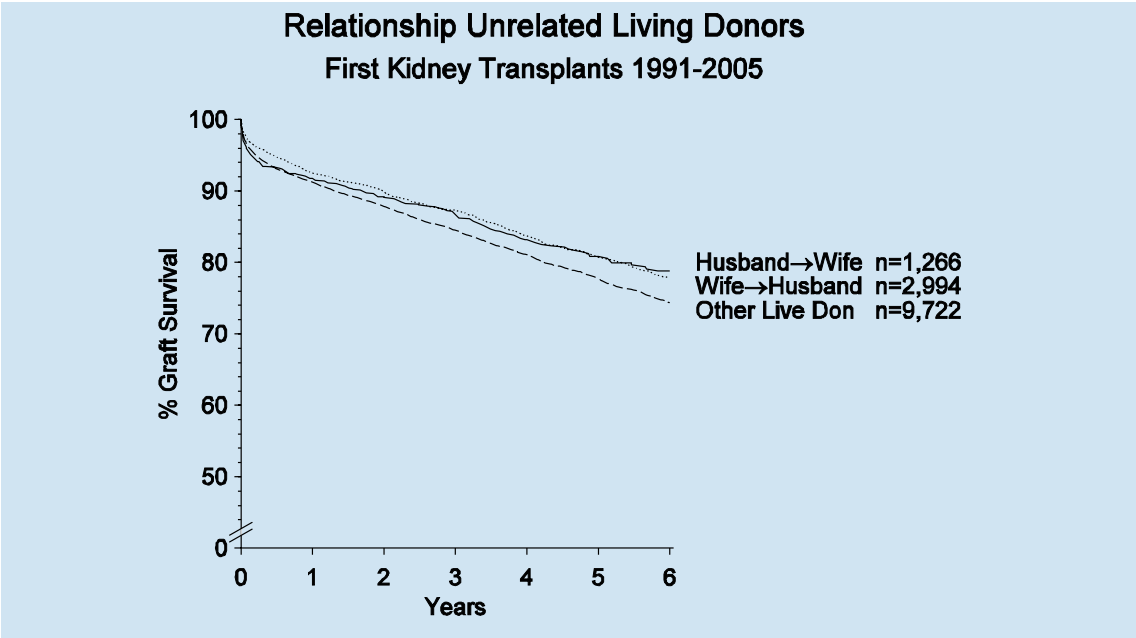
Husband-to-wife and wife-to-husband transplantations performed between 1991 and 2005 show virtually identical results with a 3-year graft survival of 87% (Figure 6). If a wife recipient has been pregnant, the outcome may be worse (3).

Figure 6: Graft survival in living unrelated kidney transplantation



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10.1.2 Patient survival

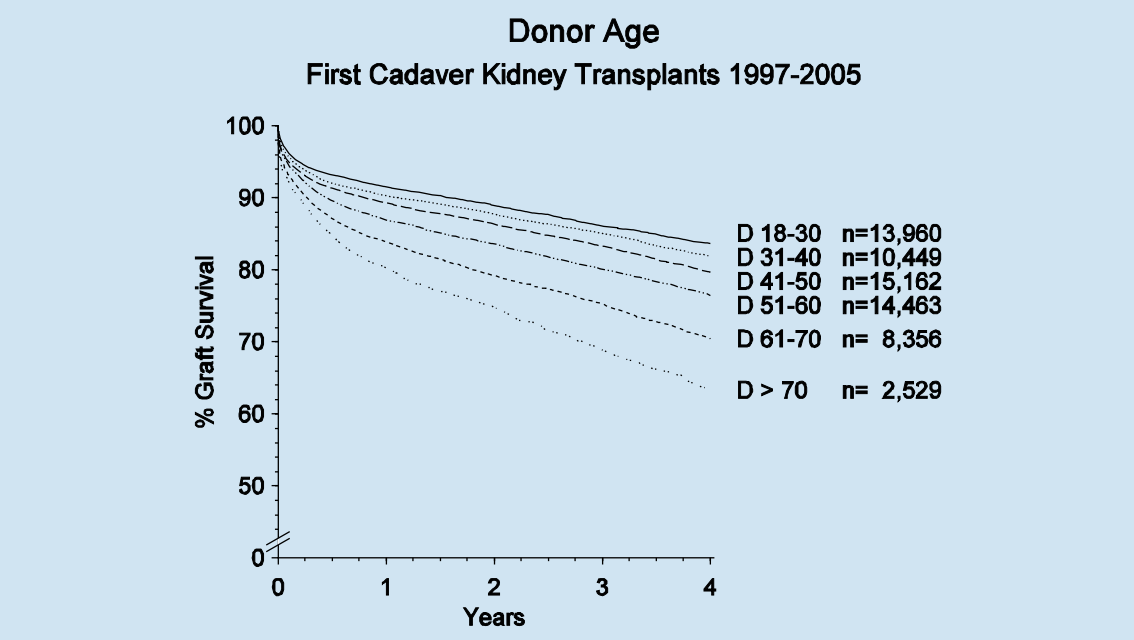
Nowadays, patient survival following living-donor kidney transplantation is about 98% after 1 year and 90% after 5 years. This is better than patient survival following deceased donor kidney transplantation with a 1-year survival rate of 95% and a 5-year survival rate of about 80% (1, 2).

10.2 Age of donor and recipient

10.2.1 Donor's age

The donor's age has a highly significant influence on the outcome of kidney transplantation in deceased-donor transplantation. With increasing age of donor (except in paediatric transplantation), there is a worsening of initial function, long-term function and survival rate. The 3-year graft-survival rate of a deceased-donor transplant is up to 20% higher for donors aged 18-30 years than for donors older than 70 years (Figure 7) (1, 2, 4).

Figure 7: Impact of donor's age on graft survival in deceased-donor kidney transplantation



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Other than in deceased-donor transplantation, donor's age appears to influence graft outcome only marginally in living-donor transplantation (4). The most likely interpretation of this difference is that living donors are selected for organ donation based on their general status of health whereas such selection is not made in the case of deceased donor transplantation. Furthermore, it is likely that the process of brain death, which is associated with the release of cytokines, chemokines, etc, further contributes to the lower success of grafts from elderly deceased donors.

10.2.2 Recipient's age

The recipient's age has an important impact on transplant outcome (5). Five-year graft survival in recipients aged 18-34 years is 72% versus 59% in recipients more than 65 years old (2). Nevertheless, the transplantation of kidneys from old donors to old recipients is feasible with acceptable success rates (6). The importance of HLA-matching is not clear in this 'old for old' group.

10.3 HLA-matching

Despite impressive improvements in graft success rates in recent years (Figure 1), the 'relative' impact of HLA compatibility on graft outcome has not changed. Between 1995 and 2004, the relative risk for graft loss was 0.77 for 0-1 HLA-A+B+DR mismatches and 1.17 for 5-6 HLA-A+B+DR mismatches. These relative risk values were almost identical with the 0.76 and 1.16 values calculated for 0-1 and 5-6 mismatches, respectively, for transplantations between 1985 and 1994 (7, 8).

According to UNOS, in patients transplanted between 1997 and 2005, recipients of 0 HLA-A+B+DR mismatched deceased-donor kidneys showed an 11% lower 5-year graft survival than recipients of 6

mismatched kidney transplants which is similar to the CTS data (Figure 8). Also similar to the findings in the CTS database, UNOS data confirm that graft outcome gradually worsens with every additional mismatch (2). HLA matching is still important even with 'modern' immunosuppressive agents such as tacrolimus, MMF, rapamycin, or IL-2 receptor antibodies (Figure 9). It is still debatable whether HLA-DR compatibility influences graft outcome more than compatibility for HLA-A+B.

Figure 8: Impact of HLA compatibility on deceased-donor kidney graft survival

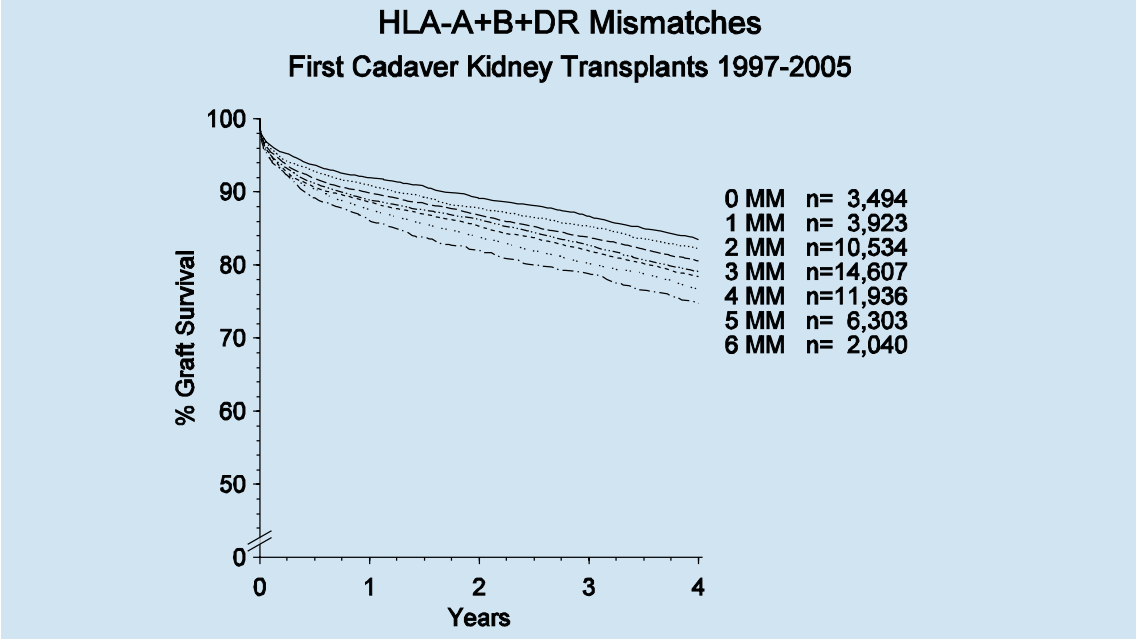

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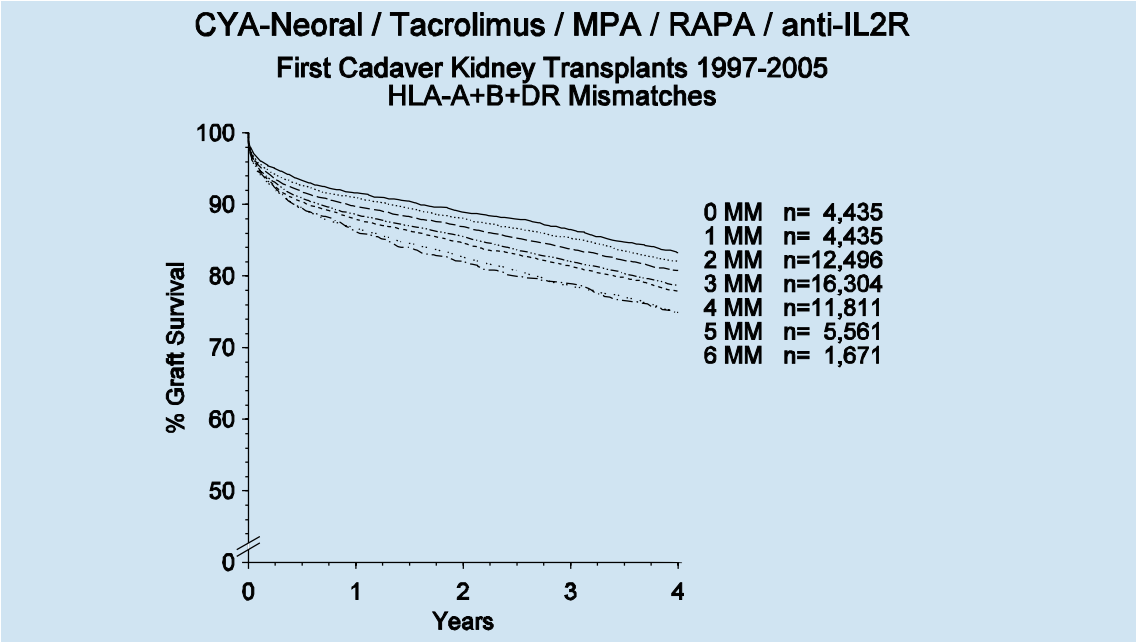
Figure 9: Impact of HLA compatibility on kidney graft survival under 'modern-day' immunosuppression



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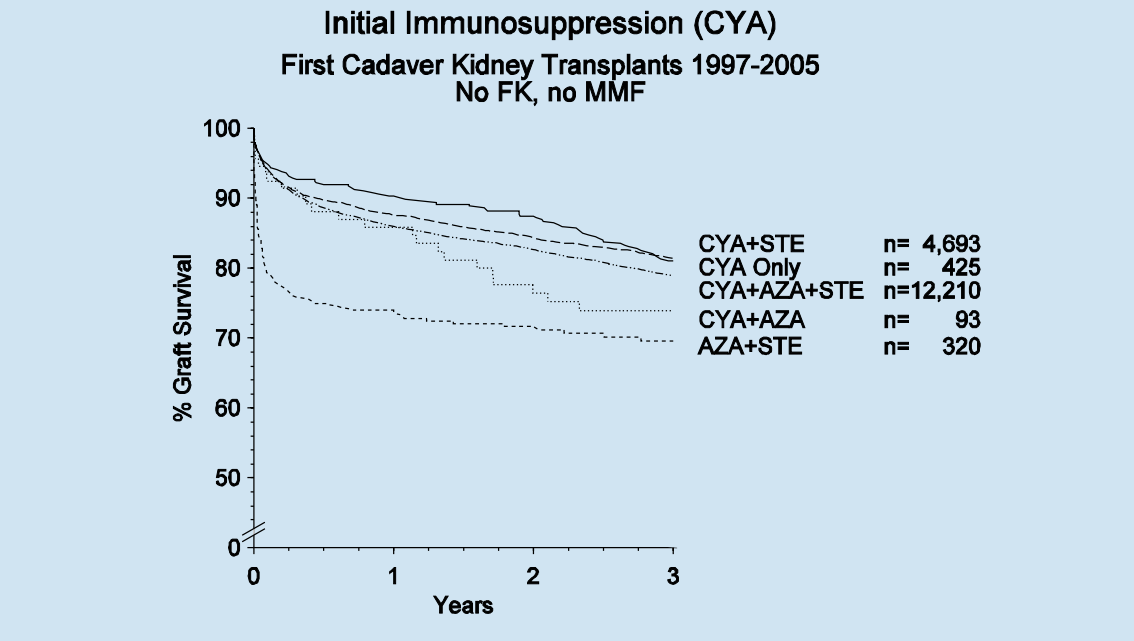
CYA = cyclosporine A; MPA = mycophenolate mofetil; RAPA = rapamycin.

10.4 Immunosuppression

Data from the CTS study clearly demonstrates the advantage of cyclosporine A-based immunosuppression. Graft-survival rates are about 15% superior to survival rates following immunosuppression without

cyclosporine A (Figure 10). However, different combinations of 'modern' immunosuppressive drugs do not appear to result in major differences in graft outcome (Figure 11).

Figure 10: Influence of cyclosporine A-based immunosuppression on kidney graft survival in first transplant recipients



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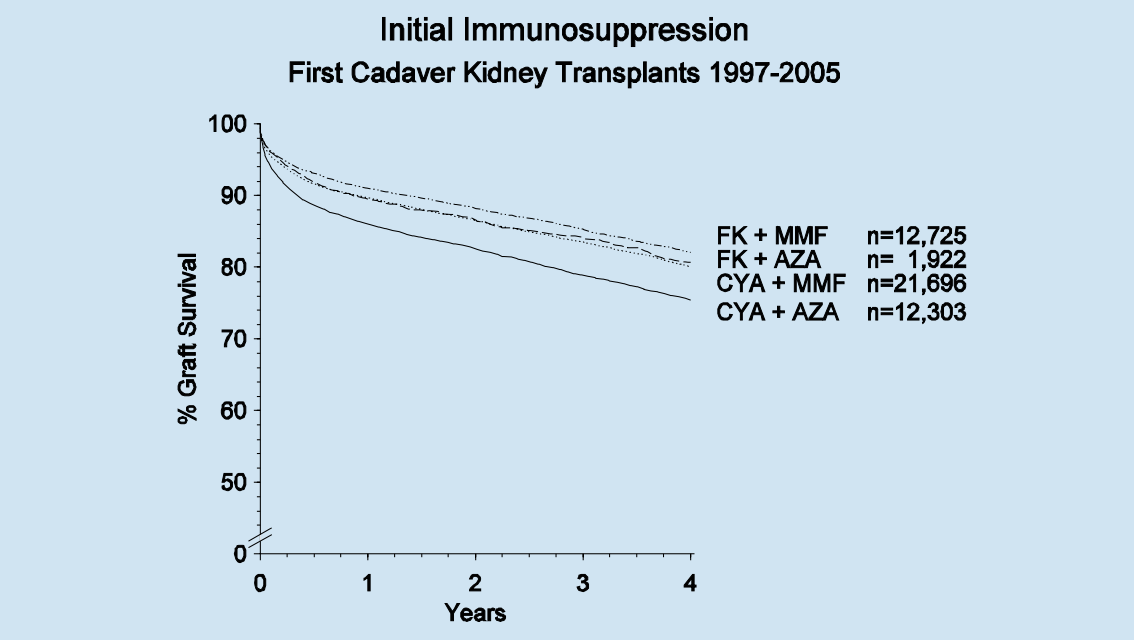
FK: FK506; MMF: mycophenolate mofetil; CYA = cyclosporine A; AZA = azathioprine; STE = steroids

Figure 11: Influence of different immunosuppressive agent combinations on graft survival following kidney transplantation



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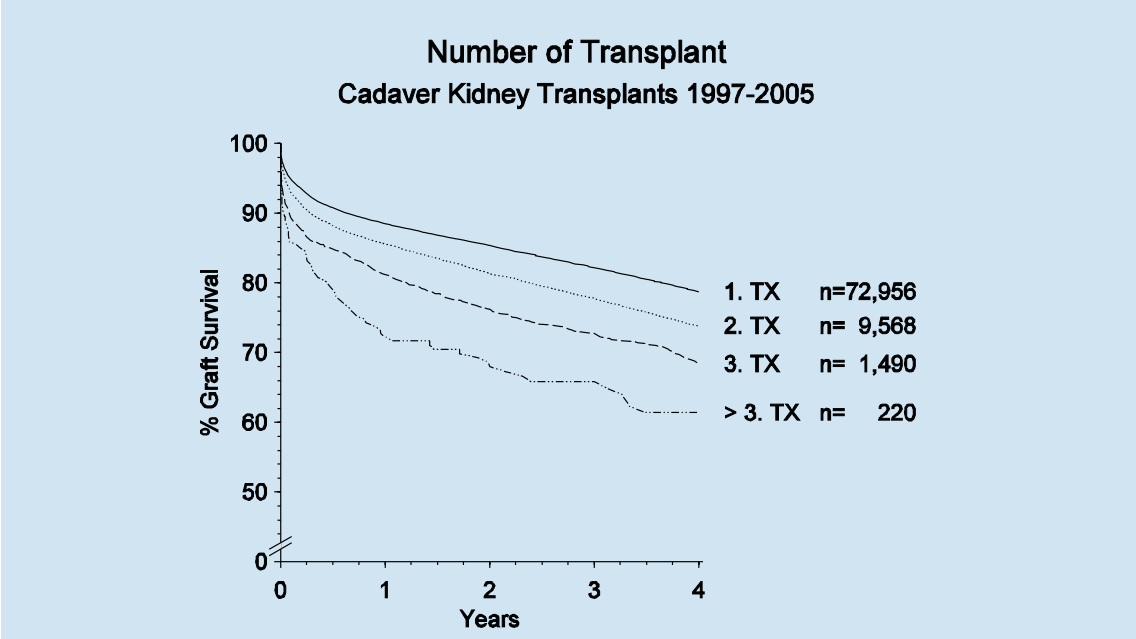
CYA = cyclosporine A; FK: FK506; AZA = azathioprine; MMF: mycophenolate mofetil.

10.5 Number of transplantations

The 4-year graft survival rate decreases by about 5% from the first to second and second to third transplantation. The 4-year graft survival rate for the first deceased-donor transplantation is 80% versus 75%

for the second, 70% for the third and 63% for the fourth or more transplants (Figure 12). For living donors, the worsening of graft function between first and second transplantation is less marked (about 2%) (1).

Figure 12: Number of transplantations and kidney graft survival



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10.6 Cold ischaemia time

The success of unrelated living-donor kidney transplantation suggests that short cold ischaemia time plays an important role in kidney transplantation. However, according to CTS data, graft survival is influenced only marginally by ischaemia times up to 24 h (Figure 13) and that HLA matching has a significant effect on outcome, even with a short ischaemic preservation time (Figure 14). Compared to other preservation solutions, University of Wisconsin (UW) solution was associated with significantly better outcome in the CTS study with ischaemia > 24 h (7).

Figure 13: Impact of cold ischaemia time on graft survival in deceased-donor kidney transplantation

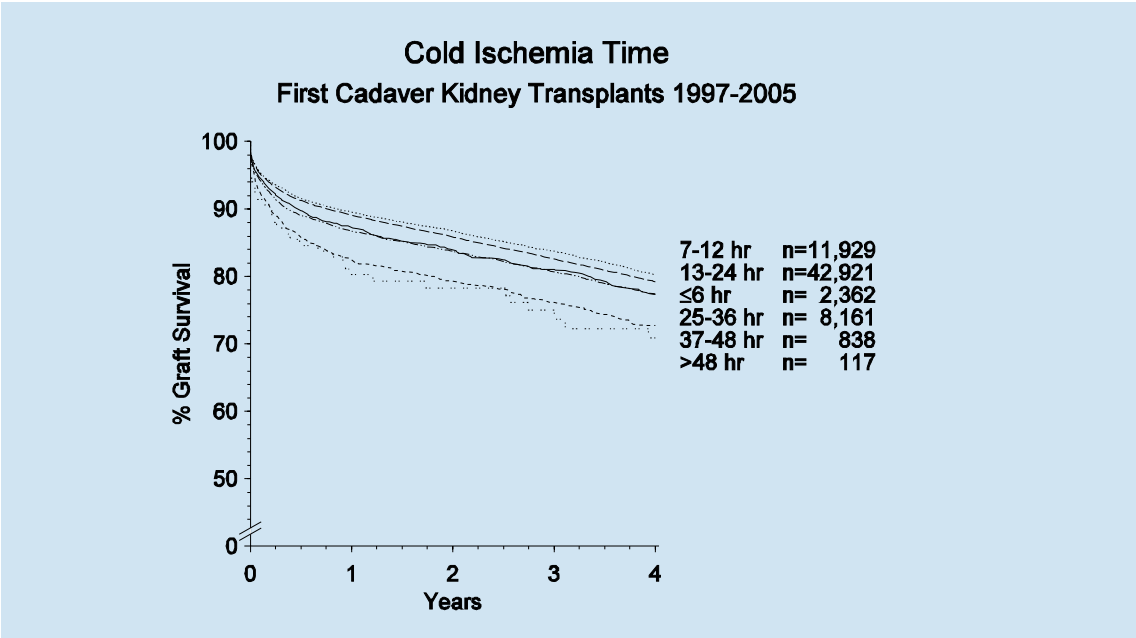

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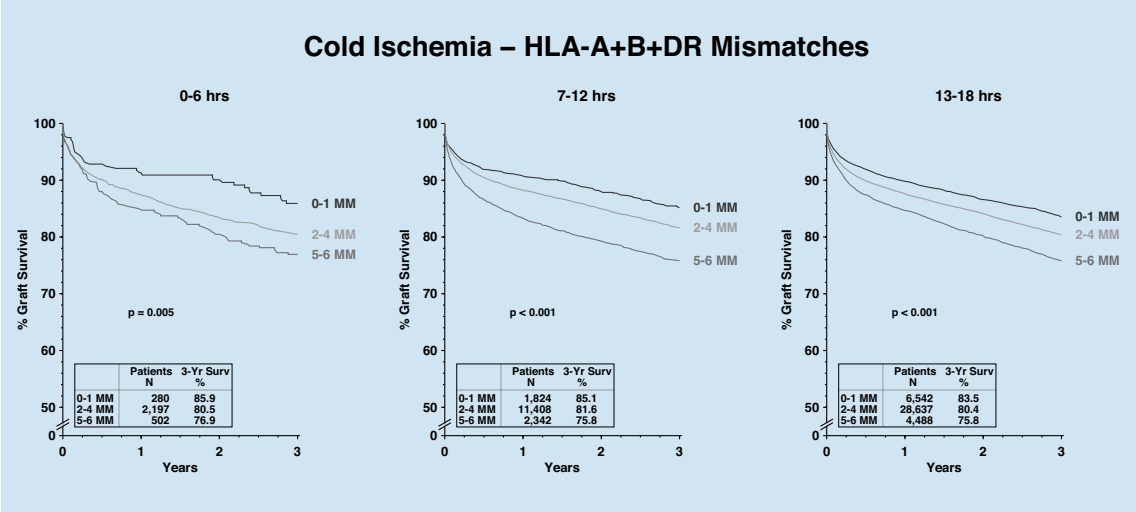
Figure 14: HLA-match dependent impact of cold ischaemia time on graft survival in deceased-donor kidney transplantations performed between 1990 and 2005



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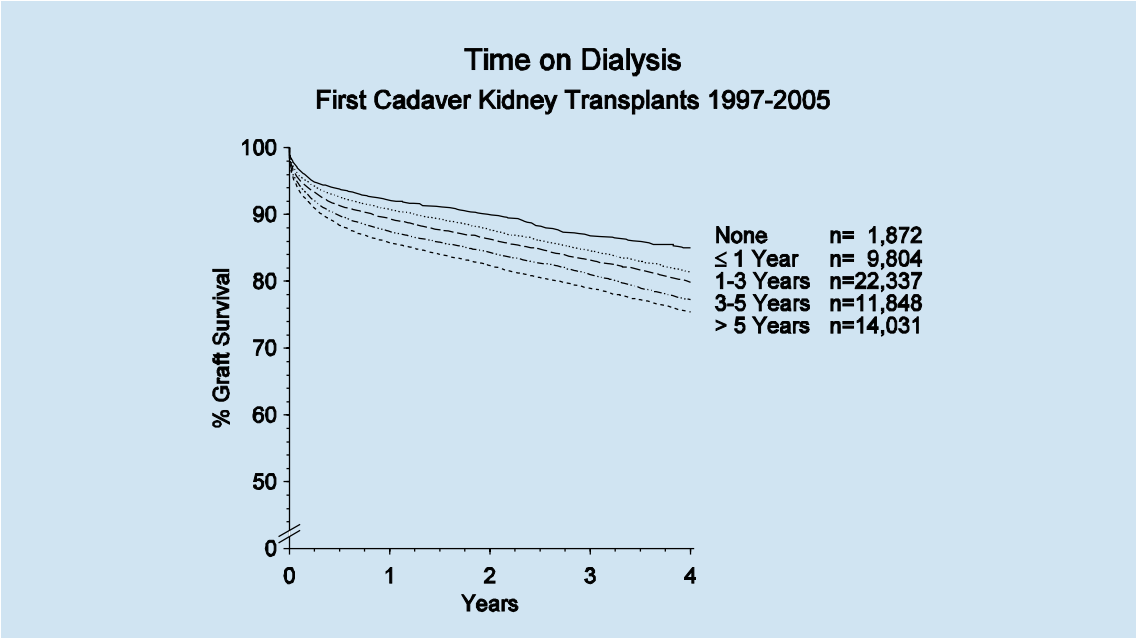
10.7 Time on dialysis

According to CTS data, graft outcome is best if the patient never received dialysis and diminishes with every additional year of dialysis treatment (Figure 15). These findings are in agreement with data from reports that underline the importance of pre-emptive transplantation (9).

Figure 15: Impact of time on dialysis on graft survival in deceased-donor kidney transplantation



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11. ABBREVIATIONS USED IN THE TEXT

This list may not include the most commonly known abbreviations

ABO	blood group system consisting of groups A, AB, B and O
ACD	acid-citrate-dextrose
ACE	angiotensin-converting enzyme
ACKD	acquired cystic kidney disease
ACR	acute cellular rejection
ADPKD	autosomal dominant polycystic kidney disease
AHG	anti-human globulin
AHR	acute humoral rejection
ALG, ATG	anti-lymphocyte globulin
AM	acceptable mismatch
Anti-GBM	anti-glomerular basement
AVF	arterio-venous fistula
AZA	azathioprine
BMI	body mass index
CAR	chronic allograft rejection
CDC	complement-dependent cytotoxicity test
CMV	cytomegalovirus
CNIs	Calcineurin-inhibitors
CsA-ME	cyclosporine A micro-emulsion
CT	computed tomography
CTS	Collaborative Transplant Study
CYA	cyclosporine A
DTT	dithiothreitol (test)
DRE	digital rectal examination
EAU	European Association of Urology
EBV	Epstein-Barr virus
EC	EuroCollins (solution)
EC-MPS	enteric-coated mycophenolate sodium
EDTA	ethylenediaminetetra-acetic acid
EDHEP	European Donor Hospital Education Program
ELISA	enzyme-linked immunosorbent assay
ESRD	end stage renal disease
ESWL	extracorporeal shockwave lithotripsy
ET	Eurotransplant
FSGS	focal and segmental glomerulosclerosis
GFR	glomerular filtration rate
GR	grade of recommendation
HAR	hyper-acute rejection
HbA1C	glycosylated haemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCA	human leucocyte antigen
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen, histocompatibility antigen
HTK	histidine-tryptophan-ketoglutarates
IF	interstitial fibrosis
IL-2	interleukin-2
IMPDH	inosine monophosphate dehydrogenase (inhibitors)
IVIG	intravenous immunoglobulin
LCDD	light-chain deposit disease
LE	level of evidence

LLDN	laparoscopic live donor nephrectomy
LURD	living unrelated donor
MMF	mycophenolate mofetil
MPA	mycophenalic acid
MR	magnetic resonance
MRT	magnetic resonance tomography
NHBD	non-heartbeating donor
OKT3	anti-CD3 monoclonal antibody
OLDN	open live donor nephrectomy
PBS	phosphate-buffered sucrose
PRA	panel-reactive antibody
PSA	prostate-specific antigen
PTLD	post-transplantation lymphoproliferative disease
RAPA	rapamycin
RCC	renal cell carcinoma
ST	Scandia Transplant
STE	steroids
TA	tubular atrophy
TB	Tuberculosis
UNOS/OPT	United Network for Organ Sharing/The Organ Procurement and Transplantation Network
UW	University of Wisconsin (solution)
VATER	Vertebrae, Anus, Trachea, Esophagus, and Renal
WHO	World Health Organization

Conflict of interest
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