

# Eau Guidelines on Renal Transplantation<sup>☆</sup>

T. Kälble<sup>a,\*</sup>, M. Lucan<sup>b</sup>, G. Nicita<sup>c</sup>, R. Sells<sup>d</sup>, F.J. Burgos Revilla<sup>e</sup>, M. Wiesel<sup>f</sup>

<sup>a</sup>Department of Urology, Städt. Klinikum Fulda, Philipps-University Marburg Pacelliallee 4, D-36043 Fulda, Germany

<sup>b</sup>Clinical Municipal Hospital, Cluj-Mapoca, Romania

<sup>c</sup>University of Florence – Hospital, Firenze, Italy

<sup>d</sup>Royal Liverpool University Hospital, Liverpool, United Kingdom

<sup>e</sup>Hospital Ramón y Cajal, Madrid, Spain

<sup>f</sup>University of Heidelberg, Heidelberg, Germany

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## Abstract

**Objectives:** To produce a guidelines text, on behalf of the European Association of Urology, providing insights in the issues surrounding renal transplantation.

**Method:** A group of international experts in renal transplantation carried out a non-structured literature review on available medical databases and urological literature.

**Result:** A guideline text is presented providing an overview of key issues involved in the patients' management such as assessment of donors, pre-transplant evaluation, techniques, management, post-transplant care, etc.

**Conclusion:** The current text represents a consensus statement developed by a group of international experts in renal transplantation.

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**Keywords:** Kidney donation; Renal transplantation; Complications; Immunosuppressants; EAU guidelines

## 1. Introduction

Chronic kidney disease is a global public health problem of growing proportions. End-Stage Renal Disease (ESRD) is defined as permanent loss of the kidneys' ability to filter wastes from the circulatory system. ESRD can result from a number of medical conditions, the most prevalent being diabetic nephropathy closely followed by vascular nephropathies, glomerulonephritis, polycystic kidney disease and interstitial nephritis; the latter three are less common and data shows that their incidence has not significantly changed over time.

Renal transplantation is now widely considered the treatment of choice for patients with ESRD due to improved short- and long-term survival benefits over

dialysis treatment. One has to keep in mind that as yet no long-term follow-up data is available for all new immunosuppressants such as mycophenolate mofetil (MMT), tacrolimus (TAC) and sirolimus. In this field of non-nephrotoxic, selective immunosuppressants for transplantation we may expect to see new developments in the coming years.

## 2. Patient and donor selection for renal transplantation

### 2.1. Living donors: 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 herpes virus, human immunodeficiency virus (HIV-1 and 2) and hepatitis B surface antigen (HBsAg), hepatitis C (HCV)-positive serology, acute hepatitis, cytomegalovirus (CMV), Epstein-Barr virus (EBV) (only in pae-

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\* Corresponding author. Tel. +49 661 845 951; Fax: +49 661 845 952.  
E-mail address: t.kaelble.urologie@klinikum-fulda.de (T. Kälble).

diatric recipients), viral infection, sepsis, tuberculosis, infections of unknown aetiology, family history of (or clinical signs that may be caused by) Creutzfeldt-Jacob disease, and active syphilis.

Urinalysis and culture, along with 24 h urine collection for creatinine clearance and protein excretion, are included as part of the routine evaluation. If there is any concern regarding a borderline hypertensive blood pressure, it should be measured on at least three, and as many as 10, separate occasions.

Renal arteriography is mandatory with an excretion phase to visualize the collecting system. Such testing can be performed on an out-patient basis.

Donors are judged unsuitable for a variety of reasons (Table 1). 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 be an indication of underlying renal disease. A history of thromboembolism or thrombophlebitis places a potential donor at increased risk of pulmonary embolism and therefore may exclude donation. This also is true for patients with advanced heart disease or a history of malignant neoplasia. Obesity may be a relative contraindication for any potential donor more than 30% above ideal body weight.

**Malignant tumours:** Active cancer or a history of breast carcinoma, melanoma, leukaemia, or lymphoma in the donor is an absolute contraindication to transplant. When a potential donor has experienced a brain haemorrhage of unknown aetiology, metastasis as the cause of intracranial bleeding must be excluded.

With other cancers, if less than 10 years have elapsed since completion of treatment, only life-saving transplants are recommended. Successful renal trans-

**Table 1**

Exclusion criteria for living donors

Absolute contraindications

- Age <18 years
- Uncontrolled hypertension
- Diabetes mellitus
- Proteinuria (>300 mg/24 h)
- Abnormal glomerular filtration rate compared to normal range 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, parasitic)
- Obesity
- Psychiatric disorders

**Table 2**

Special exceptions for malignant tumours<sup>a</sup>

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

Donors affected by the following low-grade (grades 1 and 2) brain tumours are suitable for kidney donation [2]

- Low-grade astrocytoma
- Pituitary adenomas
- Epidermoid cysts
- Colloid cysts of the third ventricle
- Pilocytic astrocytomas, ependymomas
- Low-grade oligodendrogliomas (Schmidt A and B)
- Choroid plexus papillomas
- Ganglionic cell tumours (gangliomas, gangliocytomas)
- Benign meningiomas
- Craniopharyngiomas
- Haemangioblastomas (not associated with Von Hippel Lindau syndrome)
- Acoustic schwannomas
- Pineocytomas
- Well-differentiated teratomas

Potential donors affected by the following high-grade (grades 3 and 4) tumours are suitable for kidney donation only when deemed clinically urgent

- Anaplastic astrocytoma
- Anaplastic oligodendroglioma (Schmidt C and D)
- Malignant ependymomas
- Gliomatosis cerebri
- Glioblastoma multiforme
- Pineoblastomas
- Medulloblastoma
- Germ cell tumours (except well-differentiated teratomas)
- Anaplastic and malignant meningiomas
- Intracranial sarcomas
- Chordomas
- Primary cerebral lymphomas

<sup>a</sup> There is no consensus on employing 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 grounds for such a test.

plants have been performed with kidneys affected by small, low grade renal carcinomas, which were completely excised. Such recipients require very careful follow-up [1].

Special exceptions for malignant tumours are listed in Table 2.

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

Once a full evaluation has been performed, 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 [25]. Where one kidney is small or suffers a minor abnormality the donor should always be left with the "better" kidney.

## 2.2. Cadaveric donors

Greater use should be made of non-heart-beating donors (NHBDs).

A diagnosis of brain death is required when considering a comatose subject as a potential cadaveric organ donor. For each such subject, a preliminary evaluation of any pathological condition that might be transmitted to a transplant recipient is mandatory; it must then be ascertained that each organ considered for transplantation is of acceptable quality. Any donor organ affected by a potentially transmittable pathology must be discarded. Infectious diseases such as HIV, uncontrolled sepsis, tuberculosis, acute hepatitis, viral infection of unknown aetiology, and many confirmed malignant neoplasms are all criteria for excluding the donor. Drug use is also an exclusion criterion and sometimes unsafe sexual behaviour within the prior 2 months.

Authorization 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 a very important factor in establishing positive, public opinion on organ donation. Presumed consent legislation would allow many more NHBDs, where informed consent law operates however, perfusion without relatives' permission is technically an unwarranted assault.

## 2.3. Elderly donors

Today, age limits for organ donation are not fixed. Traditionally, subjects older than 55 years were considered unsuitable. The major change observed in the last 10 years regarding the age range for organ donors is the increase in the upper age limit.

The results of transplants with kidneys from donors over 65 years are almost similar to those obtained with younger organs in the short term. Although the long-term survival of kidneys from elderly donors (over 60 years) is 10–15% less than those taken from younger donors also since older donors present more co-morbidity, better results may be obtained with carefully selected older donors and shortening of the cold ischaemic time [3].

## 2.4. Marginal donors

The average cadaveric donor is older than in the past due to a decrease in deaths from traumatic causes. But in the present circumstances of a scarcity of kidneys for transplantation, the definition of an acceptable donor kidney has been enlarged [4,5].

The criteria that define this so-called 'marginal donor' kidney have not been standardized and every transplant centre must establish its own guidelines on organ acceptability. If the transplant centre uses less-

than-optimal organs from elderly donors to expand the pool of donors, the donors must be evaluated according to age, vascular conditions, renal function and comorbidity. The inferior limit for a single kidney transplant is a calculated creatine clearance >60 ml/min. If the calculated creatinine clearance is between 60 and 50 ml/min, the donor may be considered 'marginal'. If the calculated creatinine clearance is <50 ml/min, then the kidneys should not be used for single transplantation; however, otherwise unacceptable organs can be used for dual transplantation. When this policy is established, it is necessary to inform the patients on the waiting list. They, in turn, must confirm their acceptance of a suboptimal organ or even of an eventual double graft.

Marginal kidney transplants have a significant survival benefit when compared with maintenance dialysis [6], and although long-term results are worse, with short-term results being more satisfactory, it seems logical to utilize older kidneys for older recipients [7,8]. This is particularly indicated in regional transplant programs where ischaemic time can be kept to a minimum. Obviously, waiting-list patients, especially older people, should be informed about the risks and benefits of the marginal donor programs. Patients over 60 years old should be offered the possibility of a graft from a marginal donor.

## 3. Patient selection and refusal criteria

Co-morbid conditions, such as diabetes mellitus or cardiovascular disease, are known to have a major impact on the morbidity and mortality of kidney transplant patients [9]. Death with a functioning kidney allograft has been shown to occur in up to 42% of kidney-transplanted patients [10], with cardiac death being the most important cause.

Nevertheless, renal transplantation in comparison to dialysis offers a survival benefit for uraemic patients with cardiovascular disease.

### 3.1. Cardiovascular disease

Since dialysis patients have an excessive risk of cardiovascular disease, a careful work-up has to be performed in every kidney transplant candidate [11]. This includes:

- Echocardiography to detect valvular disease, cardiomyopathy, and systolic and/or diastolic left ventricular dysfunction.
- Exercise electrocardiogram and/or exercise thallium scintigraphy or stress echocardiography in patients with a low exercise capacity.

- Coronary angiography in every suspected case of coronary disease, especially in elderly and diabetic dialysis patients. Revascularization, either surgical or by coronary angioplasty and/or stenting, should be performed in every suitable transplant candidate [12].

*Peripheral arterial disease* is common in uraemic patients. In potential kidney transplant recipients, very severe pelvic vessel disease may be a significant cause of technical graft failure and may enhance the risk of limb amputation [13]. Duplex sonography of the peripheral arteries and radiography of the pelvis should be done routinely before transplantation.

### 3.2. Diabetes mellitus

Patients with diabetes mellitus have an increased mortality and a reduced long-term graft outcome compared to non-diabetic patients following kidney transplantation. Nevertheless, different studies have shown that diabetes mellitus per se is not a contraindication for kidney transplantation [14]. Furthermore, isolated kidney transplantation, or combined kidney-pancreas transplantation, reduces the long-term morbidity and mortality of uraemic diabetic patients when compared to dialysis.

### 3.3. Age

Reduced mortality in transplanted patients compared to patients on the waiting list aged over 65 years has been shown [15]. A prolonged waiting time in this patient subgroup significantly decreases the beneficial

clinical outcome and the socio-economic advantages of early transplantation. Thus, every effort should be taken to reduce waiting time in this subgroup.

### 3.4. Recurrence risk (original renal disease)

Histological recurrence of original renal disease in a transplanted kidney often occurs. Depending upon the original disease, recurrence rates vary widely. The overall better life expectancy and quality of life in transplanted patients compared to dialysis patients, even in transplanted patients with recurrent disease, should be pointed out to the patient. It is only with some rare diseases that a high recurrence rate associated with a poor prognosis is a contraindication for kidney transplantation (e.g., light-chain deposit disease). Table 3 lists the recurrence rates of the most important diseases.

### 3.5. Infection risk

Infections can be a major cause of morbidity and mortality in transplanted patients. Pre-transplant recognition of potential infectious foci is therefore mandatory to avoid life-threatening conditions after transplantation.

All possibly infected transplant candidates should be seen by an ear, nose and throat specialist, dentist, dermatologist, urologist and gynaecologist (as appropriate) to rule out infectious foci. Other infections routinely screened prior to transplantation are HBV, HCV, tuberculosis, cytomegalovirus and *Treponema pallidum*.

**Table 3**

Recurrence rates and graft survival with recurrent disease (Courtesy of Dr. O. Hergesell, Department of Nephrology, University of Heidelberg)

Disease	Recurrence rate	Graft survival with recurrent disease	Treatment options
IgA-glomerulonephritis	50% after 5 years ~100% after 20 years	15% lower graft survival 5 years post transplant	ACE inhibitors (cyclophosphamide, highdose steroids in crescentic IgA-glomerulonephritis)
Focal and segmental glomerulosclerosis	15–50% early recurrence (within the first weeks after transplantation)	50–85% graft loss within two years	Cyclosporine (Plasmapheresis)
Membranous nephropathy	20–30%	~60% graft failure 4 years after diagnosis of recurrence	ACE inhibitors?
Diabetic nephropathy	Histological changes occur in 100% in the years post transplant; however, overt nephropathy does not usually occur earlier than 8 years post transplant	2% graft loss due to overt diabetic nephropathy	Antidiabetics ACE <sup>a</sup> inhibitors
Lupus nephritis	Recurrence rare	Good	Increasing immunosuppression usually not indicated
Henoch-Schonlein purpura	18% clinical recurrence (proteinuria and haematuria)	~55% after 2 years (prognosis in adults worse)	Cyclophosphamide?
ANCA <sup>b</sup> + vasculitis	~17%?		Cyclophosphamide, steroid boluses

<sup>a</sup> ACE inhibitor: angiotensin-converting enzyme inhibitor.

<sup>b</sup> ANCA: antineutrophil cytoplasmic antibody.

In particular, testing of HBV and HCV serology is very important, because viral hepatitis is the major cause of liver disease after renal transplantation and contributes to post-transplant morbidity and mortality.

Hepatitis C-positive renal transplant recipients are at increased risk of death compared with HCV-negative patients. Nevertheless, overall mortality is lower in transplanted HCV-positive patients than in HCV-positive patients on the waiting list. HCV-positive patients should be considered for a liver biopsy prior to transplantation to enable the planning of possible antiviral therapy.

### 3.6. Carcinomas

Transplant candidates, particularly over 50 years old, should be screened for pre-existing cancer. An active neoplasia in the recipient is a contraindication for kidney transplantation because of the risk of metastasis and dissemination, while a prior history of cancer does not always exclude the possibility of transplantation. However, it can be difficult to decide, in the absence of active disease, when the patient should be considered suitable for transplantation. The risk of relapse depends on the type of tumour and the length of time between the treatment of the cancer and the time of kidney transplantation.

## 4. Matching donors and recipients

### 4.1. Cross matching and histocompatibility (HLA) matching

Transplant outcome correlates with the number of HLA mismatches [16]. HLA matching should concentrate especially on HLA antigens, which have been shown to have an impact on rejection rates after transplantation. The HLA-A, HLA-B and HLA-DR phenotypes should be tested for in all potential recipient patients and donors. Kidneys from cadaveric donors should be allocated to potential recipients with the lowest number of mismatches at these HLA loci. This is also true for living donor transplantation, though HLA-compatibility seems to play a less important role in graft outcome than with cadaveric kidney transplantation. This may be because, in living donor transplantation, other risk factors for graft rejection (e.g., cold ischaemia time) can be minimized.

### 4.2. Cross matching

To avoid hyper-acute rejection of kidney transplant T-cells, a cross match test must be performed before each kidney transplantation. Routinely, a lymphocytotoxicity assay is used (detection of complement-depend

ent lymphocytotoxicity). T- and B-cell cross matches are performed, with B-cell cross match being more sensitive for class II antigens (HLA-DR antigens).

It is important to be aware of false-positive cross match results, especially in patients with autoimmune diseases who often exhibit circulating autoantigen-antibodies of the IgM class. Flow cytometry cross match may be used to confirm positive cross match results and should be available, especially in recipients with a high risk of acute rejection, including children and sensitized patients with pre-existing circulating antibodies [17].

Circulating anti-HLA antibodies have to be regularly checked for in transplant recipients (every 3 months) [18]. Pre-existing HLA-antibodies in potential transplant recipients may be due to blood transfusions, previously performed organ transplantations, or prior pregnancies.

More specific and sensitive assays have been developed for HLA-antibody testing (e.g., flow cytometry and enzyme-linked immunosorbent assay (ELISA)-based methods) to detect anti-class II antibodies and non-complement fixing antibodies (e.g. IgG2).

### 4.3. ABO blood group matching

Since ABO antigens behave as strong transplant antigens (i.e., expression on renal vascular endothelium), an ABO mismatch leads to early hyper-acute rejection and must be avoided.

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 used for transplantation in A, B or AB recipients. In living donor transplantation, ABO compatibility is as acceptable as ABO identity. Matching of ABO blood group antigens is instrumental in preventing HAR.

### 4.4. Viral disease

#### 4.4.1. Cytomegalovirus (CMV)

Testing of cytomegalovirus infection status is necessary to define the risk of developing CMV disease in the recipient and to plan prophylactic treatment and post-operative surveillance. In CMV IgG antibody-negative recipients who have received a transplant from a CMV-positive donor, adequate prophylaxis with oral ganciclovir is strongly recommended as the risk of primary CMV is very high.

#### 4.4.2. HBV and HCV infection

HCV-negative recipients should not receive HCV-positive kidneys. Whether or not HCV-positive recipients can receive HCV-positive organs is still a matter of debate because of concerns about long-term morbidity and mortality. Transplant recipients with HBsAg-posi-

tive infection should be monitored very closely after renal transplantation, using liver function testing and the measurement of viral replication by HBV DNA, the same applies to Hepatitis C-positive patients.

## 5. Procedure

### 5.1. Pre-transplant therapy: abnormal urinary tract

In patients whose end-stage renal disease is caused by either a congenital malformation (i.e., posterior urethral valve, spina bifida, prune belly, vesico-ureteric reflux, bladder extrophy, VATER-Syndrome, renal anomalies/radical dysplasia or an acquired malformation (i.e., tuberculosis, neurogenic, repeated surgery for vesico-ureteric reflux, or by a functional disorder of the lower urinary tract) the abnormality must be corrected before transplantation, with pre-transplant urodynamic assessment being the key investigation [19,20].

In low-compliance bladders with high intravesical pressures and/or residual urine, pharmacological therapy (e.g., parasympathicolysis) and/or intermittent catheterization is necessary. If these methods fail or catheterization is not possible, supravescical urinary diversion is crucial [20,21–24]. Ureteral implantation in a fibrotic, thickened bladder wall (e.g., following urethral valves) has to be avoided due to the associated, high risk of transplant loss [19].

*Autosomal dominant polycystic kidney disease (ADPKD), medically refractory hypertension, chronically infected kidneys or renal or urothelial cancer* are indications for pre-transplant nephrectomy.

### 5.2. Surgical alternatives in living-donor nephrectomy

Depending on the surgeon's experience and preferred choice of operation, there are several ways of removing kidneys from living donors [26,27]:

- Classic transperitoneal approach, either through a midline, or through a left or right subcostal incision.
- Sub/supracostal extraperitoneal approach (left or right).
- Dorsal lumbar approach, in which the incision can be performed either underneath the 12th rib, resecting the 12th rib, or above the 12th rib (extraperitoneal, extrapleural).
- Laparoscopic approach, which can be either transperitoneal or retroperitoneoscopic.

Most European transplant centres recommend the removal of the left kidney from a living donor because of the longer length of the left renal vein. Before

**Table 4**

Advantages and disadvantages of laparoscopic live-donor nephrectomy

#### Advantages

- Less post-operative pain
- Minimal surgical scarring
- Rapid return to full activities and work (approx. 4 weeks)
- Shorter hospital stay
- Magnified view of renal vessels

#### Disadvantages

- Impaired early graft function
- Graft loss or damage during 'learning curve'
- Pneumoperitoneum may compromise renal blood flow
- Longer operative time
- Tendency to have shorter renal vessels and multiple arteries
- Added expense of instrumentation

excision the anaesthesiologist should increase the donor's diuresis, which is usually done by administering mannitol, 25 g. Arterial spasm may be improved with externally applied papaverine.

Laparoscopic kidney removal is a less traumatic technique and entails less pain, a shorter hospital stay, and has a significant effect on increasing the number of new donors who wish to help their loved ones (Table 4).

## 6. Post-operative care and immunosuppression

### 6.1. Post-operative care

Adequate post-operative analgesia is the key factor in preventing post-operative complications, such as atelectasis and pneumonia [28–30]. Infections should be minimized with appropriate antibiotic prophylaxis. Subcutaneous Heparin, the continuous use of leg stockings and sequential compression devices are advisable to prevent deep venous thrombosis of the lower limbs. Most patients tolerate oral feeding by post-operative day 2 or 3. The donor can be discharged between post-operative days 2 to 6 following laparoscopic donation. Renal function and blood pressure should be assessed periodically after operation. Donors experience a 25% increase in serum creatinine level; this should return to near baseline by 3 months after the operation.

There are no convincing data to suggest that living donors are at any increased long-term risk as a result of having donated a kidney. Nevertheless, it is reasonable to recommend ongoing periodic long-term follow-up evaluation for these patients. This can be performed by the donor's personal physician.

### 6.2. Immunosuppression

The principle underlying successful immunosuppression is 'the balance of survival', i.e., practitioners

have to prescribe a sufficient dosage of drug to suppress rejection, without at the same time endangering the life and health of the recipient. Current policies now aim at achieving acceptable 10-year graft survival.

One has to keep in mind that prophylactic immunosuppression should be continued indefinitely, although protocol variations due to switching compounds may be, and often are, necessary. Patients should be given full information pre-transplant about the need for compliance, and the outcome of the preferred immunosuppressive regime in terms of graft survival and hazard to the patient. All patients must be counselled about the risks of infection, cardiovascular disease and malignancy, all of which are heightened by current immunosuppressive regimes and particularly by repeated courses of biological agents for infection.

Initial maintenance prophylaxis, using either cyclosporine or tacrolimus-based therapy, represents current best practice pending publication of long-term results using newer agents. Blood-level monitoring of both drugs 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).

Long-term graft- and patient-survival rates in patients treated with tacrolimus plus MMF patients are not yet available to judge safety and efficacy in terms of long-term patient graft survival. Sirolimus, though effective in reducing early rejection, has not yet been evaluated for more than 3 years in prospective, controlled studies.

## 7. Primary immunosuppressive prophylaxis

### 7.1. Cyclosporine A

Modern therapy is based on cyclosporine A, used together with more recent drugs, such as MMF which has replaced azathioprine. Prednisolone is still regarded by the majority of practitioners as a fundamental adjunct to primary immunosuppression, although prednisolone withdrawal has been possible. Cyclosporine is nephrotoxic in the majority of patients, and its long-term use may be a cause of chronic allograft nephropathy.

### 7.2. Tacrolimus

In the early 1990s, this drug became the main competitor to cyclosporine A. It is a calcineurin inhibitor like cyclosporine A, and is therefore also associated with nephrotoxicity, though less commonly than cyclosporine. Blood monitoring levels of these two drugs are therefore mandatory to prevent both over-

dosing, leading to nephrotoxicity, and underdosing, which may lead to rejection. Tacrolimus is associated with prevalence for diabetes of 20% compared with 4% for cyclosporine.

### 7.3. Mycophenolate mofetil

There is well-documented evidence that MMF reduces the incidence of biopsy-proven acute rejection after transplantation, as shown by large, multi-centre, randomized, prospective, controlled studies [31–34].

MMF is now routinely used as a primary- or second-line therapy instead of Azathioprine in many units where Azathioprine is usually reserved only for those patients who cannot tolerate MMF.

Azathioprine and MMF should never be co-administered.

Recently published data indicates that co-administration of MMF with cyclosporine, with or without prednisolone, allows a reduction or cessation of macro-lide dosage [35].

*Sirolimus* was licenced for clinical use in 1999 by the FDA and as an adjunct to cyclosporine therapy in Europe in 2002. The drug, a non-nephrotoxic, broadly reactive anti-proliferative for rejection, has been found to act synergistically with, and be equipotent to, cyclosporine. It shows dose-dependent, reversible thrombocytopenia and hypercholesterolaemia [36].

Long-term follow-up has not yet been reported with Sirolimus. Though its record as a potent agent against early rejection seems impressive, it is not yet known whether a reduction in CAN will be a longterm result of its use.

## 8. Complications

### 8.1. Immunological complications

Rejection is the commonest cause of early and late transplant dysfunction. There is a great variation in the tempo and severity of rejection episodes and the response to treatment for them. Determining factors are the degree of sensitization to HLA, as measured by the panel reactive antibody (PRA) and the history of previous rejection episodes, the degree of HLA mismatch, particularly in sensitized recipients [37], non-compliance with immunosuppressive treatment, and some virus infections, e.g., CMV. The main types of immunological reactions are:

- Hyper-acute rejection (HAR): Antibody-mediated rejection is caused by pre-formed anti-HLA or anti-AB (blood group) antibodies.

**Table 5**

T-cell mediated acute cellular rejection

**Tubulo-interstitial rejection**

- The typical histological hallmarks are infiltration by T-cells, macrophages, and to a lesser extent, neutrophils
- The presence of plasma cells is associated with a poorer prognosis [38]

**Type II endarteritis**

- Histological injury to graft capillaries and small intra-renal vessels is seen in 35–60% of patients with an ACR [39]
- This histological feature must be distinguished from fibrinoid necrosis, which is more typical of cyclosporine toxicity

**Glomerular lesions**

- These occur in 7% of biopsies and represent an unusual variant of rejection
- They are sometimes associated with viral infections (i.e., HCV, CMV) [40]

**Table 6**

Pathological classification of renal allograft lesions [42]

**Categories of immunological rejection**

- A. Hyper-acute rejection (HAR)
- B. Acute allograft rejection
  1. T-cell mediated (acute cellular rejection, ACR)
    - a. Tubulo-interstitial (Banff Type I)
    - b. Endarteritis (Banff Type II)
    - c. Glomerular (acute allograft glomerulopathy)
  2. Antibody-mediated (acute humoral rejection)
    - a. Capillary (peritubular ± glomerular)
    - b. Arterial (fibrinoid necrosis; Banff type III)
- C. Chronic allograft rejection (CAR; humeral or unknown pathogenesis)
  1. Tubulo-interstitial
  2. Vascular (chronic allograft arteriopathy)
  3. Glomerular (chronic allograft glomerulopathy)

ACR: acute cellular rejection; CAR: chronic allograft rejection.

- **Acute cellular rejection (ACR):** This is far more common, occurring in 40–70% of cases. It can occur from 5 days post transplant onwards, and is most likely to occur within the first 3 months, although it may occur thereafter. Acute allograft rejection can be classified into either T-cell mediated (acute cellular rejection, ACR) or antibody mediated (acute humoral rejection) (Table 5).
- **Chronic rejection:** This slowly progressive destruction of the graft is caused by fibrosis and arteriosclerosis and is of uncertain aetiology. It is probably the commonest cause of graft failure up to 10 years post transplant, affecting up to 25% of donor grafts [41].

The gold standard for the diagnosis of ACR and chronic allograft rejection (CAR) is transplant biopsy. Uniform criteria, known as the Banff criteria, have been agreed (Table 6), and form the basis for deciding prognosis and treatment.

### 8.2. Chronic allograft rejection (CAR, humoral or unknown pathogenesis)

Twenty-five per cent of patients will lose their grafts due to chronic allograft nephropathy (CAN), a sizeable but unknown number of which will have chronic allograft rejection (CAR) [41].

Chronic allograft rejection 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. The main differential diagnosis is chronic nephrotoxicity, which is common in patients receiving calcineurin inhibitors and

chronic allograft nephropathy in a marginal donor kidney.

Chronic allograft nephropathy (CAN) is the commonest cause of long-term graft loss, and is caused by CAR, macrolide toxicity, hyperfiltration (or a marginal donor kidney) and rarely pyelonephritis.

### 8.3. Malignancy

The incidence of neoplasia in transplanted patients is higher than in the general population, and is an important cause of morbidity and mortality in transplanted patients [43]. The presence of a neoplasia in the recipient can be due to:

1. A prior malignancy in the recipient: known or latent.
2. Transmission of a donor neoplasia to the recipient.
3. Development of a new tumour in the recipient.

The risk of recurrence after kidney transplantation of pre-existing malignancies is given in Table 7.

Immunosuppression may stimulate the growth of dormant metastases, and patients can develop recurrences of tumours treated more than 5 years prior to transplantation. Thus, although many centres demand a cancer free interval of 2 years prior to transplantation for most tumours, the length of the waiting period should be individualized according to the type of tumour. A shorter waiting period may be sufficient, with little being gained in some tumours by demanding a cancer-free interval of more than 1 year. However, with invasive cancers having a poorer prognosis, 5 years could be recommended [44,45].

**Table 7**

Risk of recurrence of pre-existing malignancies following kidney transplantation

Risk of recurrence
Low risk (0–10%)
<ul style="list-style-type: none"> <li>• Incidentally discovered RCC</li> <li>• Lymphomas</li> <li>• Testicular, uterine, cervical, thyroid cancer</li> </ul>
Intermediate risk (10–25%)
<ul style="list-style-type: none"> <li>• Endometrial cancer</li> <li>• Wilms' tumour</li> <li>• Colon, breast and prostate cancer</li> </ul>
High risk (>25%)
<ul style="list-style-type: none"> <li>• Bladder cancer</li> <li>• Sarcomas</li> <li>• Skin cancer</li> <li>• Symptomatic RCC</li> <li>• Myelomas</li> </ul>

Patients who remain on the waiting list for prolonged periods should be thoroughly evaluated yearly to make sure that they have not developed malignancy that may preclude or delay transplantation.

## 9. Conclusion: graft and patient survival

Graft survival after living-donor kidney transplantation is better than with cadaver-kidney transplantation, even for unrelated donors with six mismatches. The 1-year graft survival of living-donor kidney is at least 95% for HLA-identical siblings and 90% for 1-haplotype-identical related donors, compared with 80% for cadaver kidneys. The 3-year graft survival of living-donor kidney transplantation is 90% for HLA-identical siblings, 80–85% for 1-haplotype-identical related, 85% for spouses, and at least 80% for living, unrelated, unmarried donors, compared with 70% for cadaver kidneys.

Patient survival following living-donor kidney transplantation is at least 95% after 1 year and 90% after 5 years. This is better than patient survival following cadaver kidney transplantation with a 1-year survival rate of 90% and a 5-year survival rate of about 80% [46–50] (Table 8).

The donor's age has a highly significant influence on the outcome of kidney transplantation. With increasing age of the donor (except in paediatric transplantation), there is a worsening of initial function, long-term function and survival rate. For living donors, the outcome of kidneys from donors older than 65 years is

**Table 8**

Advantages of living donation

- Better results (both long- and short-term) compared to cadaver 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

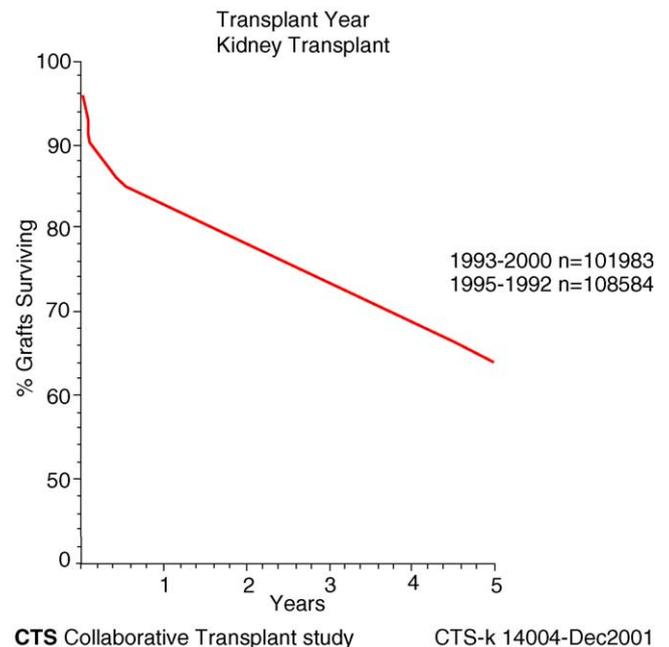


Fig. 1. Graft survival following kidney transplantation. (Courtesy of Prof Dr G. Opelz, Heidelberg). The above general outcome following kidney transplantation depends on several criteria of which some are discussed below.

only slightly worse than for kidneys from donors younger than 65 years (Fig. 1) [49,51,52].

In addition, the recipient's age has an important impact on the outcome of transplantation [53].

Nevertheless, the transplantation of kidneys from old donors to old recipients is very feasible with a good success rates. It is not clear yet how important it is to have HLA matching in this 'old for old' group [54].

Even with 'modern' immunosuppressive agents, including the drugs tacrolimus (FK 506), MMF (Cellcept), sirolimus, rapamycin, or interleukin-2 (IL 2) receptor antibodies, HLA matching continues to be important [55]. In particular, HLA-DR matching is important with nearly 10% difference in graft survival between 0 and 2 mismatches of HLA-DR [49,50]. In the presence of good HLA matches, the shorter the ischaemia time, the better is graft survival [56].

## References

- [1] Penn I. Precautions to be taken to prevent transmission of neoplastic diseases in the grafting process. In: *Organ and Tissue Transplantation in the European Union*. London: Graham and Trotman; 1994. p. 33–41.
- [2] Council of Europe International Consensus. Committee of experts on the organisational aspects of co-operation in organ transplantation. Standardisation of organ donor screening to prevent transmission of neoplastic diseases. Strasbourg: Council of Europe Publishing; 1997.
- [3] Gridielli B, Remuzzi G. Strategies for making more organs available for transplantation. *New Engl J Med* 2000;343:404–10.
- [4] Alexander JW, Vaughn WK. The use of ‘marginal’ donors for organ transplantation. The influence of donor age on outcome. *Transplantation* 1991;51:135–41.
- [5] Johnson LB, Kuo PC, Dafeo DC, Schweitzer EJ, Alfrey EJ, Klassen DK, et al. Double adult renal allografts: a technique for expansion of the cadaveric kidney donor pool. *Surgery* 1996;120:580–3 [Discussion 583–4].
- [6] Ojo AO, Hanson JA, Meier-Kriesche B, Okechukwu CN, Wolfe RA, Leichtman AB, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and waitlisted transplant candidates. *J Am Soc Nephrol* 2001;12:589–97.
- [7] Basar B, Soran A, Shapiro R, Vivas C, Scantlebury VP, Jordan ML, et al. Renal transplantation in recipient over the age of 60: the impact of donor age. *Transplantation* 1999;67:1191–3.
- [8] European best practice guidelines for renal transplantation (Part 1). Transplantation Section II: evaluation and selection of donors. *Nephrol Dial Transplant* 2000;15(Suppl 7):39–51.
- [9] Braun WE, Marwick TH. Coronary artery disease in renal transplant recipients. *Cleve Clin J Med* 1994;61(5):370–85.
- [10] Weinrauch L, D’Elia JA, Healy RW, Gleason RE, Christleib AR, Leland OSJ. Asymptomatic coronary artery disease: angiographic assessment of diabetics evaluated for renal transplantation. *Circulation* 1978;58:1184–90.
- [11] Lindholm A, Albrechtsen D, Frödin L, Tufveson G, Persson NH, Lundgren G. Ischemic heart disease—major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation* 1995; 60: 451–7.
- [12] de Lemos JA, Hills LD. Diagnosis and management of coronary artery disease in patients with end-stage renal disease on hemodialysis. *J Am Soc Nephrol* 1996;7:2044–54.
- [13] Jassal SV, Krahn MD, Naglie G, Zaltzman JS, Roscoe JM, Cole EH, et al. Kidney transplantation in the elderly: a decision analysis. *J Am Soc Nephrol* 2003;14:187–96.
- [14] Holley JL, Monaghan J, Byer B, Bronsther O. An examination of the renal transplant evaluation process focusing on cost and the reason for patient exclusion. *Am J Kidney Dis* 1998;32:567–74.
- [15] Kasiske BL, Ramos EL, Gaston RS, Bia MJ, Danovitch GM, Bowen PA, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Patient Care and Education. Committee of the American Society of Transplant Physicians. *J Am Soc Nephrol* 1995;6(1):1–34.
- [16] Opelz G, Wujciak T, Dohler B. Is HLA matching worth the effort? Collaborative Transplant Study *Transplant Proc* 1999;31:717–20.
- [17] European best practice guidelines for renal transplantation (Part 1). *Nephrol Dial Transplant* 2000;15(Suppl 7):1–85.
- [18] Kasiske BL, Ramos EL, Gaston RS, Bia MJ, Danovitch GM, Bowen PA, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Patient Care and Education Committee of the American Society of Transplant Physicians. *J Am Soc Nephrol* 1995;6:1–34.
- [19] Adams J, Gudemann C, Mohring K, Mehls O, Wiesel M. Renal transplantation in children with malformations of the urinary tract. *Transplant Proc* 2002;34:726–7.
- [20] Crowe A, Cairns HS, Wood S, Rudge CJ, Woodhouse CR, Neild GH. Renal transplantation following renal failure due to urological disorders. *Nephrol Dial Transplant* 1998;13:2065–9.
- [21] Ebert A, Boswald M, Schott G, Rosch WH. Transplantation in children with congenital anomalies of the lower urinary tract. *Akt Urol* 2001;32:266–72.
- [22] Hatch DA, Koyle MA, Baskin LS, Zaontz MR, Burns MW, Tarry WF, et al. Kidney transplantation in children with urinary diversion or bladder augmentation. *J Urol* 2001;165:2265–8.
- [23] Koo HP, Bunchman TE, Flynn JT, Punch JD, Schwartz AC, Bloom DA. Renal transplantation in children with severe lower urinary tract dysfunction. *J Urol* 1999;161:240–5.
- [24] Power RE, Calleary JG, Hickey DP. Pre-transplant bilateral native nephrectomy for medically refractory hypertension. *Ir Med J* 2001;94:214–6.
- [25] Lucan M, Rotariu P, Iacob G, Ghervan L, Lapusan Carmen, Sarb D. Renal grafts with anatomic anomalies—a solution to extend the pool of living donors. In: *Abdominal Organ Transplantation from Living Donors: State of the Art, 21–23 June 2002*. Gubbio, Italy. Abstracts volume, p. 85.
- [26] Lucan M. Actualities in renal transplantation. In: *Dragomirescu C, Popescu I. Actualities in Surgery [Romanian]*. Bucuresti: Celsius; 1998. p. 243–50.
- [27] Lucan M. Experience with living donor renal transplantation in Romania [German]. In: *Fahlenkamp D, Schonberger B, Tufveson GA, Loening SA. Podium Urologie, Band 3, Living donor Renal transplantation*. Berlin: Blackwell Wissenschafts-Verlag; 1997. p. 151–8.
- [28] Lucan M. *Textbook of Surgical Urologic Techniques [Romanian]*. Bucuresti: Infomedica; 2001. p. 1111–4.
- [29] Yanaga K, Podeta LG, Broznick B, Shapiro R, Stieber A, Makowka L. Multiple organ recovery for transplantation. In: *Starzl TE, Shapiro R, Simmons RL, editors. Atlas of Organ Transplantation*. New York: Gower; 1992. p. 1–49.
- [30] Eklund B, Eklund P, Lindfors O, Lindstrom BL. Living donor nephrectomy: surgical aspects. *Scand J Urol Nephrol* 1981;64:157–61.
- [31] The European Mycophenolate Mofetil Co-operative Study Group. Placebo controlled study of Mycophenolate Mofetil combined with cyclosporine and corticosteroids to the prevention of acute rejection. *Lancet* 1995;345:1321–5.
- [32] Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric allograft recipients. *US Renal Transplant Mycophenolate Mofetil Study Group. Transplantation* 1995;60:225–32.
- [33] The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation 1996. *Transplantation* 1996;61:1029–37.
- [34] The European Mycophenolate Mofetil Co-operative Study Group. Mycophenolate mofetil in renal transplantation: three-year results from the placebo-controlled trial. *Transplantation* 1999;68:391–6.
- [35] Abramowicz D, Manas D, Lao M, Vanrenterghem Y, Del Castillo D, Wijngaard P, et al. Cyclosporine Withdrawal Study Group. Cyclosporine withdrawal from a MMF-containing immunosuppressive regimen in stable kidney transplant recipients: a randomised controlled study. *Transplantation* 2002;74:1725–34.
- [36] Johnson RWG, Kreis H, Oberbauer Brattstrom C, Claesson K, Esis J. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001;72:777–86.
- [37] Morris PJ, Johnson RJ, Fuggle SV, Belger MA, Briggs JD. Analysis of factors that affect outcome of primary cadaveric renal transplantation in the UK. HLA Task Force of the Kidney Advisory Group of the

- United Kingdom. Transplant Support Service Authority (UKTSSA). *Lancet* 1999;354:1147–52.
- [38] Charney DA, Nadasdy T, Lo AW, Racusen LC. Plasma cell-rich acute renal allograft rejection. *Transplantation* 1999;68:791–7.
- [39] Bates WD, Davies DR, Welsh K, Gray DW, Fuggle SV, Morris PJ. An evaluation of the Banff classification of early renal allograft biopsies and correlation with outcome. *Nephrol Dial Transplant* 1999;14:2364–9.
- [40] Cosio FG, Roche Z, Agarwal A, Falkenhain ME, Sedmak DD, Ferguson RM. Prevalence of Hepatitis C in patients with idiopathic glomerulonephathies in native and transplant kidneys. *Am J Kidney Dis* 1996;28:752–8.
- [41] Hostetter TH. Chronic transplant rejection. *Kidney Int* 1994;46:266–79.
- [42] Mauiyyedi S, Baid S, Pascual M, et al. Chronic allograft glomerulopathy related to hepatitis C virus infection. *Mod Pathol* 2000;13:176.
- [43] Buell J, Trofe J, Hanaway MJ, Lo A, Rosengard B, Rilo H, et al. Transmission of donor cancer into cardiothoracic transplant recipients. *Surgery* 2001;130(4):660–6 discussion, 666–668.
- [44] European best practice guidelines for renal transplantation (Part 1). *Nephrol Dial Transplant* 2000;15(Suppl 7):6–7.
- [45] Penn I. The effect of immunosuppression on pre-existing cancers. *Transplantation* 1993;55(4):742–7.
- [46] British Transplantation Society. Towards standards for organ and tissue transplantation in the United Kingdom. 1998:25. Published by the British Transplantation Society, London, United Kingdom.
- [47] Cecka JM. The UNOS Scientific Renal Transplant Registry. *Clin Transpl* 1998;1–16.
- [48] EBPG (European Expert Group on Renal Transplantation); European Renal Association (ERA-EDTA); European Society for Organ Transplantation (ESOT European best practice guidelines for renal transplantation (Part 1). *Nephrol Dial Transpl* 2000;15(Suppl 7):83–5.
- [49] Opelz G. Collaborative Transplant Study—10-year report. *Transplant Proc* 1992;24:2342–55.
- [50] Opelz G. Impact of HLA compatibility on survival of kidney transplants from unrelated live donors. *Transplantation* 1997;64:1473–5.
- [51] Ivanovski N, Popov Z, Kolevski P, Cakalaroski K, Spasovski G, Stankov O, et al. Kidney transplantation using living donors over age 65. *Ann Urol Paris* 2000;34:302–5 [French].
- [52] Terasaki PI. The HLA-matching effect in different cohorts of kidney transplant recipients. *Clin Transpl* 2000;497–514.
- [53] Morris J, Johnson RJ, Fuggle S, Belger MA, Briggs JD. Analysis of factors that affect outcome of primary cadaveric renal transplantation in the UK. *The Lancet* 1999;354:1147–52.
- [54] Voiculescu A, Schlieper G, Hetzel GR, Hollenbeck M, Ivens K, Willers R, et al. Kidney transplantation in the elderly: age-matching as compared to HLA-matching: a single center experience. *Transplantation* 2002;73:1356–9.
- [55] CTS Collaborative Transplant Study. Newsletter 2001; 3(September).
- [56] CTS Collaborative Transplant Study. Newsletter 2002; 1(March).