# GUIDELINES ON RENAL TRANSPLANTATION

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## Introduction

As attitudes and practice to renal transplantation (RT) vary significantly the Guidelines provide general guidance only.

## Kidney donation

There is a widening gap between donation and demand for kidney transplants, with not enough deceased donors. There is, however, a clear trend towards an increase in living-donor transplants.

| **Recommendations for increasing donation** | **GR** |
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| **Deceased donors** | |
| In all countries without 'presumed consent' law, increase efforts to recruit donors through an opting-in register or by carrying donor cards. | C |
| Greater use of non-heart-beating donors (NHBD) should be made. Create policies for recently dead admissions to casualty departments which may be used as NHBDs. | B |
| Use of carefully selected donors > 60 years should be encouraged as a continuing source of deceased-donor kidneys. | B |
| Organs from deceased donors > 70 years should be individually evaluated. | B |

| Living donors | |
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| Organ donation should be considered a charitable gift. Society can express gratitude to organ donors for their gift (e.g. 'Medal of Honour', donor insurance). | C |
| Explore living donation when a patient first presents with end-stage renal disease. | C |
| Decisions about multiple renal artery or grafts with anatomical anomalies should be made on an individual basis. | C |
| Laparoscopic nephrectomy offers similar results (complications, graft function and graft survival) compared to open nephrectomy, with less post-operative morbidity, shorter convalescence and better cosmetic results. | A |
| Laparoscopic nephrectomy increases the number of people willing to donate. | C |
| Paired kidney exchange, if permitted by national law. | C |

### Kidney donor selection and refusal criteria

The physical condition of the donor, especially of the organ to be donated, is more important than age. 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 single- rather than multi-organ donations include previous myocardial infarction, coronary bypass angina, severe systemic vascular disease and long-lasting hypotension, oliguria, and a long period in intensive care.

The potential donor should be assessed for human immunodeficiency virus-1, -2 (HIV-1, HIV-2), hepatitis C virus (HCV) and hepatitis B surface antigen (HBsAg), anti-hepatitis B core (anti-HBc) antibody, acute hepatitis (liver enzymes), cytomegalovirus (CMV), Epstein-Barr virus if the recipient is paediatric, active syphilis, other viral infections, sepsis, tuberculosis,

infections of unknown aetiology, and a family history (or possible clinical signs) of Creutzfeldt-Jacob disease.

Different circumstances apply when a recipient is already infected with HIV or hepatitis and transplant from infectious donors is possible in certain situations.

A previous history of malignancy need not be a contraindication for organ donation. However, absolute contraindications are active cancer, or a history of metastatic cancer (with a few exceptions, e.g. testicular cancer), and cancers with high recurrence rates, e.g. lymphoma. Exclude metastasis as a cause of intracranial bleeding in a potential donor with a brain haemorrhage of unknown aetiology. For special exceptions in malignancy, consult the full Guidelines.

Kidneys from marginal donors must have a calculated creatinine clearance rate (CrCl) of 50-60 mL/min. Kidneys with CrCl < 50 mL/min are only suitable for dual transplant.

| **Recommendations for brain dead donors** | **GR** |
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| Consider every brain-dead comatose subject as a potential organ donor, without age limits. | |
| Obtain agreement for organ harvesting from relatives (significant others) according to local law and policies. Authorisation for explantation by the donor's close relatives is always recommended, even if local legislation presumes consent. | |
| Always exclude individuals who objected to donation during life. | C |
| A donor organ affected by a potentially transmissible pathology (infections, neoplasias) must be carefully evaluated considering the risk/benefits for the recipient. | B |

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| A good-quality organ must be guaranteed to the recipient and every transplant centre must establish its own guidelines on organ acceptability. Marginal organs can only be used after thorough assessment. Counsel recipients and confirm their acceptance. | C |

| **Surgical techniques** | **GR** |
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| Living-donor transplantation is associated with higher success rates than deceased-donor transplantation. | B |
| The surgeon is responsible for making sure the donor is medically and psychologically suitable, the donated organ is healthy, and success in the recipient is likely. | B |
| Always leave the donor with the 'better' kidney. The transperitoneal approach carries a higher risk of splenic and intestinal complications. | 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 |

## Kidney recipient

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.

| Recommendations for pre-transplant therapy | GR |
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| In the 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 impossible, urinary diversion is necessary using catheterisable pouches, conduits, or cystoplasties. | B/C |
| Remove kidneys with autosomal-dominant polycystic kidney disease if there is insufficient space or complications (chronically infected kidneys, or kidneys with suspected tumour growth). | B/C |

### Other special considerations in a recipient

| Recommendations | GR |
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| Active malignancy is a contraindication because immunosuppression may aggravate underlying malignancy jeopardising the patient's life and graft outcome. | B |
| The waiting period before transplantation in recipients with a history of malignancy depends on the type, TNM stage and grade of the tumour, age, and general health. | B |
| Active infection may exacerbate after transplantation and may be life-threatening. | B |
| Screen for viral and bacterial diseases in all transplant candidates including hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), and tuberculosis (TB). | |

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| Routine screening examination of all patients in all subspecialties is not necessary. However, a patient with history and symptoms suspicious for an underlying active infection should be seen by the appropriate specialist (e.g. ear, nose, and throat specialist; dentist; dermatologist; urologist and/or gynaecologist) to firmly rule out infectious foci. | B |
| Re-evaluation of non-compliance (and serious morbidity) may be appropriate. | C |
| The pre-transplant work-up should focus on looking for cardiac disease. The work-up should be extensive in patients at high risk of cardiac disease to firmly rule out coronary artery disease. Perform any revascularisation before transplantation. | B |
| Peripheral artery disease is common in uraemic patients. Special attention should be paid to iliacal, peripheral, and cerebrovascular disease using appropriate diagnostic and therapeutic measures. | C |
| Patients with diabetes mellitus should be transplanted. They require an extensive pre-transplant work-up. | B |
| Obesity itself is not a contraindication for transplantation. A thorough pre-transplant evaluation and attempt to reduce weight are recommended. | C |
| Patients at risk of coagulopathies should be carefully evaluated to prevent early post-transplant thrombotic events. | C |
| Diseases that might influence post-transplant course (e.g. diverticulosis, cholecystolithiasis, hyperparathyroidism) should be identified during pre-transplant work-up and if possible treated before transplantation. | C |
| Age itself is not a contraindication, but the recipient must undergo a thorough pre-transplant evaluation and risk-benefit assessment and be counselled about the increased risks associated with age. | B |

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| Recurrence of the original renal disease is common, though graft loss due to recurrence is not. Only a few rare diseases with a high recurrence rate leading to early graft loss are contraindications for transplantation. Patients at risk of recurrent disease should be counselled especially before living related-donor transplantation. | C |

## Matching of donors and recipients

| Recommendations | GR |
|---|---|
| Determine ABO blood group and HLA-A, -B, and -DR phenotypes of all candidates awaiting transplantation. | B |
| To avoid hyper-acute rejection (HAR), cross-matching must be performed before transplantation. | B |

Kidneys from deceased donors should be allocated to recipients with the lowest number of HLA mismatches. False-positive results for cross-matching may occur especially in autoimmune diseases. Potential recipients with a high percentage of panel-reactive antibodies (%PRA) can be further analysed to ensure a negative cross-match. ABO blood group matching prevents HAR, but technical advances have resulted in successful ABO-incompatible transplantation.

## Immunosuppression after kidney transplantation

The current standard initial immunosuppression provides excellent efficacy with good tolerability: calcineurin inhibitor (CNI; cyclosporine or tacrolimus) + mycophenolate (mycophenolate mofetil [MMF] or enteric-coated mycophenolate sodium [EC-MPS]) + corticosteroid (prednisolone or methylprednisolone). Induction therapy may also be given.

| Recommendations for immunosuppressive therapy | GR |
|---|---|
| Rejection prophylaxis using CNIs remains current best practice. | A |
| Choice of CNI (cyclosporine or tacrolimus) depends on 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 (increased risk of rejection) and excessively high blood levels (increased risk of chronic side-effects, particularly nephrotoxicity). | A |
| Mycophenolates are the current standard of care. The standard dose of MMF combined with cyclosporine is 1 g twice daily or EC-MPS 720 mg twice daily. | A |
| Combination therapy of Mycophenolates with tacrolimus is not formally approved. Optimal mycophenolate (MPA) dosing is unclear, as tacrolimus-treated patients have a higher MPA exposure than cyclosporine-treated patients. The standard starting dose of MMF combined with tacrolimus is MMF 1 g twice daily or EC-MPS 720 mg twice daily. This dosage is often dose-reduced with 30-50% lower doses at 1 year. | A |
| MPA monitoring cannot be recommended for all patients due to limited evidence of benefit. | A |
| Azathioprine may be used in a low-risk population for initial immunosuppression, especially in patients intolerant to MPA formulations. | A |
| Initial steroid therapy remains the standard of care in perioperative and early postoperative period. | A |
| In order to reduce steroid associated side effects, steroids may be stopped in most patients after 3-12 months on combination therapy with CNI and MPA. | A |

| Recommendations for other immunosuppressive therapies | |
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| **mTOR inhibitors (sirolimus, everolimus)** | **GR** |
| Acute rejection can be effectively prevented by inhibitors of the mammalian target of rapamycin (mTOR) (sirolimus, everolimus) combined with CNIs. Reduce CNI dosage to avoid aggravated nephrotoxicity. | A |
| Initial CNI-free combination therapy of mTOR inhibitors with MPA and steroids is not sufficient to prevent acute rejection compared to a standard regimen. | A |
| Prophylactic surgical measures must be used when mTOR inhibitors are given in the perioperative period because of impaired wound healing. | A |
| mTOR inhibitors are an alternative to CNIs if there are severe CNI-related side-effects. | A |
| Blood levels of sirolimus and everolimus must be regularly monitored. | A |
| **T-cell depleting induction therapy** | |
| Potential life-threatening side-effects include a higher incidence of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease. | B |
| T-cell depleting therapy has not resulted in improved outcomes overall. | B |
| T-cell depleting therapy should not be routinely used in a low-risk first-transplant recipient. | B |
| Patients must be informed of the increased risks of infection and cancer. | B |
| **Interleukin-2 receptor antibodies (IL-2R)** | |
| They reduce the rate of acute rejection, enabling CNI- and steroid-sparing regimens. | A |

## Complications

Hyper-acute rejection (HAR) is rare and usually occurs within

minutes or hours of vascularisation, although it may occur up to 1 week post transplant. It is cured by graft removal.

Acute allograft rejection can be classified into acute cellular rejection (ACR, T-cell mediated) or acute humoral rejection (AHR, antibody-mediated). Test patients with ACR immediately for HLA IgG antibodies reactive with the graft. Steroid bolus therapy is recommended as initial treatment. In severe, or steroid-resistant, rejection, consider intensified immunosuppression, including high-dose steroid treatment, conversion to tacrolimus, and T-cell depleting agents. Treatment of AHR may include steroid bolus therapy, conversion to tacrolimus, antibody elimination and intravenous immunoglobulin treatment. Anti-CD20 (rituximab) or T-cell depleting agents may be efficacious.

Chronic allograft dysfunction may take months or years to develop. Perform a renal biopsy and determine donor-specific alloantibodies if changes develop during follow-up monitoring of serum creatinine, creatinine clearance, blood pressure, blood lipids, and urinary protein excretion. If IF/TA is confirmed, begin appropriate medical treatment, e.g. control of hypertension. Consider conversion to an mTOR inhibitor in patients under current CNI therapy and/or with histological signs suggesting CNI toxicity without significant proteinuria (< 800 mg/day). Alternatives are substantial CNI reduction under MPA protection or, in chronic maintenance patients, CNI withdrawal under MPA and steroids.

Post-transplantation cancer is a common long-term cause of death. Most malignancy affects the skin (40%) or lymphatic system (11%). Closely monitor young recipients and patients who have received T-cell depleting agents. Annual screening for cancer and co-morbidity is mandatory.

## Annual screening

Lifelong regular post-transplant follow-up by an experienced and trained transplant specialist is strongly recommended at least every 6-12 months. Monitoring of renal function and immunosuppression and side-effects by a physician, every 4-8 weeks is strongly advised.

*This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-09-0), available to all members of the European Association of Urology at their website, http://www.uroweb.org.*