GUIDELINES ON RENAL TRANSPLANTATION

T. Kälbe (chairman), M. Lucan, G. Nicita, R. Sells, FJ. Burgos Revilla, M. Wiesel

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Introduction

The number of patients registered as starting end-stage renal disease (ESRD) therapy each year has increased in all countries. The most common cause of ESRD is diabetes (affecting at least 16% of diabetes patients) closely followed by high blood pressure, glomerulonephritis, polycystic kidney disease and interstitial nephritis.

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 (aided by effective immunosuppressants such as cyclosporine A, mycophenolate mofetil (MMT), tacrolimus (TAC) and sirolimus.

Within Europe attitudes and practices concerning renal transplantation differ significantly. This text can only provide general practice guidelines rather than taking national legislation into account.

Evaluation Criteria

Absolute contraindications are: uncontrolled hypertension, diabetes mellitus, proteinuria (> 300 mg/24 h), abnormal glomular filtration rate compared to normal range for age, microscopic haematuria, high risk of tromboembolism, medically significant illnesses (chronic lung disease, heart disease, etc), history of bilateral kidney stones.

- Assess potential donor for HIV-1 and -2, hepatitis C virus (HCV) and hepatitis B surface antigen (HBsAg), hepatitis D (HDV)-positive serology, acute hepatitis, cytomegalovirus (CMV), Epstein-Barr virus (EBV) (only in paediatric recipients), viral infection, sepsis, tuberculosis, infection of unknown aetiology, family history of (or clinical signs which may be caused by) Creutzfeldt-Jakob disease and active syphilis.
- Transplant from an HCV-positive donor to an HCV-positive recipient is permissible, but only life-saving transplants should be performed in an HCV-negative recipient (after informed consent). Kidney transplant from a HBsAg-positive donor is permissible in an HBsAg-positive recipient, or an HBsAg-negative recipient with anti-HBsAg antibody titre ≥ 10 mIU/mL, but only life-saving transplants should be performed in an HBsAg-negative recipient with no anti-HBsAg antibody (after informed consent).
- Reject donors with cancer or histories of breast carcinoma, melanoma, leukaemia, or lymphoma as well as donors who died from brain haemorrhage of unknown aetiology. However, non-melanoma, low-grade skin cancer and some CNS tumours may be acceptable. For a complete list consult the full guideline text.

- Tumours that do not contraindicate donation include basal cell carcinoma, non-metastatic spinocellular carcinoma of the skin, cervical carcinoma *in situ*, and carcinoma *in situ* of the vocal cords.
- Donors affected by selected low-grade (grades 1 and 2) brain tumours are suitable for kidney donation. However, ventriculo-peritoneal shunting is an absolute contraindication for donors affected by brain tumours of any grade. Potential recipients affected by selected high-grade (grades 3 and 4) tumours should be transplanted only when clinically urgent.

Kidney donation

Living donor transplantation has a higher success rate than cadaveric donation. The donor must be medically and psychologically suitable and the donated organ healthy. The lower limit of calculated creatinine clearance suitable for a single kidney transplant is > 60 mL/min. A 'marginal' kidney has a calculated creatinine clearance of 50-60 mL/min. Kidneys with creatinine clearance < 50 mL/min are only suitable for dual transplant. Any brain-dead comatose subject (i.e., heart-beating kidney donors) is a potential organ donor. The physical condition of the donor and of the organ to be donated is more important than donor age.

Non-heart beating donors (NHBD): novel techniques for in-situ perfusion of recently dead bodies should enable greater use of NHBD. Legal implications in many countries inhibit a wider use of this option.

Kidney recipients

Pre-transplant therapy:

In most cases, pre-existing pathologies that adversely affect graft survival are to be corrected before transplantation. These include:

- Congenital malformation or functional disorder of the lower urinary tract (pre-transplant urodynamics assessment being the essential investigation).
- Low-compliance bladders (avoid ureteral implantation in a fibrotic, thickened bladder wall since it adversely affects graft survival) bladder augmentation or continent pouches with umbilical stoma are alternatives.
- Absent bladder or sphincter insufficiency; supravesical urinary diversion such as conduit or continent pouch must be performed.
- Autosomal dominant polycystic kidney disease (ADPKD); uni- or bilateral nephrectomy is necessary if there is insufficient space for the transplant kidney or due to complications.
- Chronically infected kidneys or suspected renal or urothelial cancer.

Preoperative cardiovascular work-up is mandatory to improve organ and patient survival in the post-transplant period. Co-morbid conditions, such as diabetes mellitus and cardiovascular disease, have a major impact on morbidity and mortality of kidney transplant patients. All potential transplant candidates should be seen by an ear, nose and throat specialist, dentist, dermatologist, urologist and gynaecologist to exclude infectious foci.

Matching donors and recipients

The ABO blood group and the HLA-A,-B and -DR phenotypes should be determined for all candidates awaiting kidney transplantation.

To avoid hyperacute rejection of kidney transplants cross-matching must be performed prior to each kidney transplantation:

- **Histocompatibility (HLA) matching**
  Transplant outcome correlates with the number of HLA mismatches. HLA-A, HLA-B and HLA-DR phenotypes should be tested in all potential recipient patients and donors. Kidneys from cadaveric donors should be allocated to potential recipients with the lowest number of mismatches at HLA loci. HLA-compatibility is less important in graft outcome in living donation, possibly because other risk factors for rejection can be minimized in living donation.
- **Cross matching**
  A cross match test must be performed before each transplant to avoid hyper-acute rejection (HAR) of transplant T-cells. Routinely a lymphocytoxicity assays is used and T- and B-cell cross matches performed (B-cell cross matches are more sensitive for class II antigens [HLA-DR antigens]). Especially in patients with autoimmune disease false-positive results may occur. A flow cytometry cross match may be used to confirm positive results (especially in recipients at high risk of HAR, including children and sensitized patients with pre-existing circulating antibodies).
- **Pre-existing HLA-antibodies**
  In highly sensitized (PRA > 80%) patients, analysis of HLA antibody specificities (e.g. flow cytometry and enzyme-

linked immunoabsorbent assay (ELISA-based methods) should be carried out to select acceptable HLA patterns in the potential donor (matched antigens and acceptable mismatches), which should result in negative cross match tests.

- **ABO blood group matching**
  Matching of ABO blood group antigens is critical in preventing HAR. Kidneys from potential donors with blood group O can theoretically be used for transplantation in A, B or AB recipients. To avoid an imbalance between demand and supply in cadaveric organs, for O recipients, ABO identity is mandatory. In living donor transplantation, ABO compatibility is as acceptable as ABO identity.
- **Viral disease**
  - 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. In CMV IgG antibody-negative recipients who have received a transplant from a CMV-positive donor, adequate prophylaxis with gancyclovir is strongly recommended as the risk of primary CMV is very high.
  - HBV and HCV infection
  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-positive 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.

Complications

Renal transplant practitioners must be continuously alert for acute rejection, particularly during the first 6 months post transplant. Complications may be:

Immunological: immunological rejection is the commonest cause of early and late transplant dysfunction.

HAR is a rare complication, usually occurring within minutes or hours of surgery. Delayed HAR may occur within a week of transplant. HAR is recognized by acute anuria, fever and a swollen graft and treated by graft nephrectomy.

Acute cellular rejection (ACR): patients with ACR should be tested as soon as possible for anti-HLA IgG antibodies reactive with the graft by CDC cross matching. Patients with ACR should be treated with parenteral methylprednisolone (500 mg to 1 g), given intravenously in three, daily, pulses.

Chronic allograft rejection (CAR, humoral or unknown pathogenesis): during follow-up after renal transplantation, transplant practitioners must regularly monitor urinary protein secretion, serum creatinine and creatinine clearance. Changes in these parameters over time should trigger hospital admission for renal biopsy. If CAR is confirmed, appropriate medical treatment (e.g. control of hypertension and acidosis with ACE inhibitors) should be started.

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 due to:

- a prior malignancy in the recipient: known or latent
- transmission of a donor neoplasia to the recipient
- development of a new tumour in the recipient.

Immunosuppression following transplantation may stimulate growth of dormant metastases; tumours treated more than 5 years prior to transplantation may recur. The length of the waiting period varies according to tumour type.

Immunosuppresion

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. Prophylactic immunosuppression should be continued indefinitely. Our understanding of the mechanisms involved in immune rejection has allowed the development of safer modern immunosuppressives, which are aimed at specifically suppressing sensitized lymphocyte activity against the kidney transplant.

Cyclosporine A

Modern therapy is based on cyclosporine A, used together with more recent drugs, such as mycophenolate mofetil (MMF) instead of azathioprine. The majority of practitioners still regard prednisolone as a fundamental adjunct to primary immunosuppression, although prednisolone withdrawal may occur.

Cyclosporine is nephrotoxic in the majority of patients, and its long-term use may be a cause of chronic allograft nephropathy. Cyclosporine may also induce hypercholesterolaemia, hypertension, gum hypertrophy, hirsutism and acne.

Tacrolimus

Tacrolimus is a more powerful immunosuppressive but is associated with diabetes, neurological and electrolyte abnormalities, and nephrotoxicity. Like cyclosporine tacrolimus is a calcineurin inhibitor, but generally nephrotoxicity is less common and less severe. It is mandatory to closely monitor the levels of both drugs to prevent overdosing, leading to nephrotoxicity, as well as underdosing, which may lead to rejection.

MMF

There is well-documented evidence that MMF reduces the incidence of biopsy-proven acute rejection after transplantation. In many units MMF is now routinely used as a primary- or second-line therapy instead of azathioprine. Nowadays, azathioprine is usually reserved only for those patients who cannot tolerate MMF. Recently published data indicate that co-administration of MMF with cyclosporine, with or without prednisolone, allows for a reduction or cessation of macrolide dosage.

Sirolimus

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. Long-term follow up has not yet been reported with sirolimus.

Conclusion

Over the past decade, due to a growing number of regional and national registries for treated ESRD, more information has become available on incidence rates, prevalence and differences in the outcomes of the various treatment modalities.

Due to improved short- and long term survival of grafts, renal transplantation has become the treatment of choice for ESRD, further promoted by the introduction of new immunological suppressants.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-19-5), available to all members of the European Association of Urology at their website - http://www.uroweb.org.