Guidelines on Renal Transplantation

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**European
Association
of Urology**

TABLE OF CONTENTS   PAGE

1. INTRODUCTION

There are several national and regional registries throughout Europe involved in collecting data on end-stage renal disease (ESRD) and kidney transplantation. The European Dialysis and Transplant Association-European Renal Association (EDTA-ERA) is the only European-wide organization, alongside this range of regional and national registries.

Data shows that the number of patients on waiting lists for renal transplantation has increased in all European countries over the past decades although the patterns in growth show some variety per country. Since considerable differences exist between countries in the utilization of treatment modalities and in the selection of patients, especially related to treating older patients with associated comorbid conditions, it is difficult to compare function and survival rates. A common trend in all developed countries seems to be an increasing acceptance of patients older than 65 years as well as an increase in live donors.

The most common cause of ESRD is 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 (MMF), 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.

Since 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.

2. KIDNEY DONATION

2.1 Explantation technique

2.1.1 *Technique of cadaveric organ recovery*

RECOMMENDATIONS ON CADAVERIC KIDNEY DONATION
1. Kidneys are the last organs to be recovered in multiple organ recovery. Appropriate placement of aortic cannula for the cold 'in-situ' flush is essential (level of evidence: B).
2. After the thoracic organs and liver have been retrieved, if there is consent for the pancreas to be removed, it is advisable that the kidney and pancreas are recovered en bloc and separated on the back table (level of evidence: B). Retrieval of multiple intra-abdominal organs en-bloc, total abdominal evisceration technique prevents warm ischaemia and traction injuries to the vascular tree (level of evidence: B).
3. In multiple organ recovery, good co-ordination and co-operation between various surgical teams are essential (level of evidence: B).

The time to procure each solid organ should be minimized to decrease any unnecessary ischaemic injury. Kidney retrieval usually follows removal of the heart, lungs, liver and pancreas. The following points should be noted.
*   3L of UW (University of Wisconsin) solution are infused before organ recovery.
*   Gerota's fascia can be opened to expose the kidneys for surface cooling. While the heart is being removed and the cold perfusate is being infused, ice slush is placed into the abdominal cavity to provide surface cooling for the liver, kidneys and pancreas.
*   Once the heart is removed and the liver is to be retrieved, careful attention should be given to ensure the following:
    1. The aortic cannula should not extend beyond the ostia of the renal arteries. Such placement can result in inadequate flushing of the kidneys, leading to unnecessary warm ischaemia.
    2. In the event that the superior mesenteric artery is not 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 while the liver is being removed. 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 some risk of occluding the renal artery orifices, especially on the right side.

3.   At the time of transection of the vena cava between the liver and the kidneys, care must be taken to avoid injury to the right renal vein. The right renal vein can often extend superiorly before entering the vena cava and may be inadvertently transected. Since a segment of infrahepatic vena cava is required in liver transplantation, communication is necessary with the kidney retrieval teams to leave a desirable amount of cuff of vena cava to go with the liver and to prevent injury to the right renal vein.

4.   If consent includes retrieval of pancreas, this procedure is performed before removal of the kidneys. Again, injury to the left renal artery or vein can occur while the dissection of the pancreas is performed. 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 mobilization of the kidneys prior to their removal, especially in cases of multiple organ recovery. Such retroperitoneal dissection may cause accidental injury to aberrant renal arteries, leading to incomplete perfusion and warm ischaemia of the kidneys.

Dissection is carried cephalad and kept as far posterior as possible; the line of dissection is maintained at the level of 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 leave the kidneys during perfusion. Dissection of the kidneys can proceed with mobilization 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 mobilization 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 also be performed to minimize flushing of the liver.

If the donor is younger than 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 (5, 6) have been followed by the development of different methods of aortic infusion techniques (7-9). Such methods of recovery have allowed good organs to be obtained from NHBDs in countries that do not have brain death laws (10).

With the development of multiple organ recovery techniques (1-3), good co-ordination and co-operation between the various surgical teams involved are essential for the successful retrieval of transplantable organs (4). Logistics and programming of organ explantation should routinely be done by the local transplant coordinator.

2.1.2   The living donor

RECOMMENDATIONS ON LIVING KIDNEY DONATION
1.   The use of living donors has been associated with higher success rates than seen with cadaveric donation. Living donation allows some patients to avoid long waiting times and even dialysis (level of evidence: B).
2.   An independent assessment of the donor's renal function by a nephrologist is mandatory in all cases.
3.   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 (level of evidence: B).
4.   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.
5.   Kidney removal through a transperitoneal approach has a higher number of splenic and intestinal complications (2.3%) compared with other surgical alternatives.
6.   Open donor nephrectomy should be performed by an extraperitoneal approach through a subcostal or dorsal lumbotomy incision.
7.   Laparoscopic donor nephrectomy (either trans- or retro-peritoneal) should only be performed by those trained in this specific procedure.

At present, 20-25% of all kidney transplants in the world are performed with living donors. Most donors are genetically related. In a small but increasing percentage of cases, however, donors are genetically unrelated and include spouses, friends, or other emotionally related individuals. Ethical guidelines mandate that the living donors have not been coerced and that there is no evidence of financial profit by the donor. Living donation should be considered 'a gift of extraordinary value' (11), and should be facilitated wherever a suitable donor is available (Table 1).

Table 1: 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

2.1.2.1   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 virus (HBV) and hepatitis C virus (HCV). 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. Spiral computed tomography (CT) scanning has been used instead of conventional angiography in some centres. The use of magnetic resonance (MR) angiography is also growing in importance.

Donors are judged unsuitable for a variety of reasons (Table 2). 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 excludes donation. This is also 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.

Table 2: 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

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. Where one kidney is small or suffers a minor abnormality the donor should always be left with the "better" kidney.

2.1.2.2 Pre-operative management
Pre-operative assessment by the anaesthesiologist and the pain management team is mandatory. Although pre-operative skin cleaning is recommended, hair clipping should be avoided until just before the incision is made.

2.1.2.3 Surgical alternatives in living-donor nephrectomy
Depending on the surgeon's experience and preferred choice of operation, there are several ways of harvesting kidneys from living donors (12-14):
• 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.

Kidney removal through transperitoneal approach is used more often 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 (15-17) due to injuries of the spleen that occur during dissection of the colon. In addition, the transperitoneal approach is accompanied by a significantly higher rate of intestinal complications, such as ileus (functional or even obstructive).

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 starting the incision, the anaesthesiologist has to increase the donor's diuresis, which is usually done by administrating 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. The following are special considerations to be taken into account during a laparoscopic procedure:
• *Patient's preparation* The laparoscopic approach requires special conditions during organ harvesting, especially during dissection of the renal pedicle, when the patient requires appropriate fluids and mannitol infusion to ensure maximum renal function during surgery and in the post-operative period.
• *Patient's position on the operative table* The patient is placed 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, and on the right side the liver may make dissection difficult.
• *Transperitoneal laparoscopic approach* The transperitoneal approach offers more working space. The kidney is approached by dissecting the left colon and peritoneum on different lengths.
  The approach to the renal artery is more complicated due to its position behind the renal vein.
  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. The main drawback to this approach is the limited space for manoeuvre and the impossibility of being able to use endobags for quick kidney extraction.

2.1.2.4 Post-operative care
Adequate post-operative analgesia is the key factor in preventing post-operative complications, such as atelectasis and pneumonia (18-20). 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. Renal function 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 most reasonable to recommend ongoing periodic long-term follow-up evaluation for these patients. This can be performed by the donor's personal physician.

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2.2 Organ preservation

RECOMMENDATIONS FOR ORGAN PRESERVATION
1. EuroCollins (EC) solution is limited in use today only to living donor organs, and kidney-only cadaveric donations (level of evidence: B).
2. For multi-organ donors, UW solution is preferred, as it is the best solution for liver preservation and associated with significantly higher incidence of immediate kidney function (UW 77% vs. EC 67%) (level of evidence: A).

2.2.1 Kidney storage solutions
The major component of modern kidney storage solutions (1-6) is an impermeant solute, such as phosphate, lactobionate, glucose, sucrose or raffinose, which is used to control hypothermic swelling. There is less agreement about the need for some of the other minor components, including buffers to control acidosis, reducing agents to minimize oxidative reperfusion injury, adenine nucleotide precursors for high-energy phosphate regeneration after revascularization, and potassium and magnesium to prevent loss of intracellular cations.

Among the best known of this class of solutions are Sacks (7), Ross and Marshall (8) and phosphate-buffered sucrose (9). Currently, UW is the preferred flushing solution, as it is the best preservation solution for liver and kidneys taken from the usual multi-organ donor.

2.2.2 Methods of kidney preservation
There are two methods of kidney preservation:
- Continuous hypothermic perfusion (which is not currently necessary unless the donor is a NHBD).
- Initial flushing followed by ice storage.

2.2.3 Period of organ preservation
The period of cold ischaemia should be kept as short as possible. Organ preservation has relied heavily upon hypothermic techniques that have been developed in an attempt to lower the metabolic rate, conserve the stores of adenosine triphosphate, and prevent formation of oxygen-free radicals during the reperfusion phase. Maximum possible cold ischaemia times will be less in marginal donor or elderly kidneys.

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2.3   Policies to enhance living donation

RECOMMENDATIONS FOR POLICIES TO ENHANCE LIVING DONATIONS
1.   The gap between donation and the demand for kidney transplants is widening. Cadaveric donors are insufficient for the demand. There is, however, an increase in the number of living donors. In the USA the number of kidneys obtained from living donors has exceeded the number of kidneys obtained from cadavers. Living donation in Europe should be encouraged (level of evidence: C).
2.   Organ donation is valuable and should be considered a charitable gift. Society should express gratitude to the organ donors for their gift as is done with other charitable contributions, without jeopardizing its altruistic basis (e.g., Medal of Honour, limited reimbursement, medical leave, priority access to organ for transplant, donor insurance) (level of evidence: C).
3.   Laparoscopic nephrectomy offers donors less post-operative morbidity, quicker convalescence and better cosmetic results. It increases the number of individuals willing to donate without increasing the risk to donors' safety or allograft function (level of evidence: C). It should be used, whenever possible, only by appropriately trained and experienced surgeons.
4.   Paired kidney exchange if permitted by National Law, should be encouraged where appropriate donor/recipient pairs are available (level of evidence: C).

The rate of living donation can be increased by three methods:
*   Medical methods are represented by: 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: by showing appreciation for organ donation
*   Organizational: such as medical leave for organ donation and the reimbursement of all costs to the donor.

2.3.1   Medical methods to increase number of living donations

2.3.1.1   Acceptance of grafts with anatomical anomalies
Most experienced transplantation centers, due to the shortage of living donors, consider the contraindication for using grafts with anatomical anomalies, such as renal cysts, uretero-pelvic junction obstruction, solitary stones > 1 cm, duplex ureteral system, multiple arteries and veins, to be a relative contraindication.
        If the related donor has a good immunological correspondence with the recipient, but has an abnormal kidney, which is the only kidney available, and if the evolution of the recipient on haemodialysis is unacceptable, it is advisable to transplant the abnormal kidney leaving the donor with the best one.

2.3.1.2   Laparoscopic live donor nephrectomy (LLDN) - an alternative surgical method, which has increased the rate of living donations
Due to magnification provided by the optical system and the video camera, in experienced hands, the dissection of the renal pedicle, is more accurate by laparoscopy and, if carried out via the retroperitoneal approach, is faster and much more direct (Table 3) (7).
        The decreased size of the incision for extracting the kidney and placement of the incision in the lower abdomen, significantly reduces post-operative pain when compared with traditional open surgery. It also reduces trauma of the abdominal wall, which is followed by quicker, better healing, faster mobilization of the patient post-operatively, and quicker social reintegration. Usually, patients resume their oral intake on the first post-operative day and normal alimentation on the maximum second post-operative day. Analgesic requirements for LLDN were 30% lower than those for open procedures. Also, the need for oral pain medication was markedly reduced.
        All retrospective reviews of recipients who have received a kidney via laparoscopic donation compared with those who have received a kidney via standard open nephrectomy have shown no statistical

differences between the two groups. When compared, the populations were similar with respect to HLA mismatches, number of related donors, presence of diabetes, previous transplant, gender and race.

Overall donor complications with the laparoscopic approach have compared favourably with previously reported cases of open donation. The rate of only 1.5-2% for major complications is decreasing with the experience of the operative team. Although studies from the USA and Europe have reported that laparoscopic nephrectomy costs US $200-400 more than open procedure, patients have usually returned to employment 17 days sooner than patients who have undergone an open procedure. The cost saving to employers is more than US $4,000 per employee.

An increase of over 100% in live kidney donation has been observed in many institutions since the introduction of the laparoscopic approach. Overall, laparoscopic nephrectomy offers to donors less post-operative pain, quicker convalescence, and better cosmetic results when compared with traditional open donation. In experienced hands, this procedure is accomplished without increased risk to the donor's safety or allograft function.

Table 3: 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

2.3.1.3 Plasmapheresis and intravenous immunoglobulin: A rescue therapy for cross-match-positive living-donor kidney transplants.

A positive cross-match can present a virtually insurmountable barrier to kidney transplantation. There is a large population of highly sensitized patients who have little hope of receiving a transplant. Some from this population have potential living donors who meet standard criteria for transplantation but have a positive antihuman globulin (AHG) cross-match with their donors.

The combination of plasmapheresis and intravenous immunoglobulin under the cover of standard doses of cyclosporine, mycophenolate mofetil and steroids remove donor-specific anti-HLA antibody; and continuing B-cell suppression, with MMF or sirolimus, post-operatively has been shown to permit good graft function (8).

Keep in mind that this technique is still undergoing clinical evaluation and should not yet be generally applied to potential living donor kidney recipients until further evidence is available.

2.3.2   Ethical ways of showing appreciation for organ donation

2.3.2.1   Donor medal of honour
Organ procurement organizations could have ceremonies which recognize and appreciate the organ donation. A donor medal of honour, given by a top official of the country, would be an effective way of expressing appreciation and gratitude on behalf of the whole community to the living donors and the families of deceased donors (1, 2).

2.3.3   Organizational 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 defined by an exchange between two or more couples who are prevented by ABO incompatibility or positive cross-match from donating their kidney directly to their recipients. The problem may be solved by exchanging the living kidney donor kidneys between pairs of couples to achieve a cross-match negative or ABO compatible combination.

The donor and recipient involved in a paired kidney exchange program are interviewed separately to exclude any coercion of the donor (9). In addition, they are informed about the advantages and risks involved in

a living donation and the donor's informed consent is obtained. All donors undergo routine physical and psychological evaluation, irrespective of whether they are consanguineous or not. The inclusion criteria should favour the exchange of equivalent kidneys of a similar size and similar age.

Since 1986, when Rapaport introduced the concept of paired kidney exchange as a method for enhancing the number of living donors, this technique has been applied in several countries, including USA, Mexico, South Korea, and Japan, though rarely in Europe (i.e., Switzerland, Romania, Austria).

Many people who have wished to donate an organ to a spouse or other family member have been unable to help due to blood type incompatibility or other immunological barriers (e.g., positive cross-match).

A programme of paired kidney exchange has addressed this problem by permitting an exchange of organs from two living donors (3), or from one living donor and one deceased donor. In the later approach, recently introduced in New England, USA, a living donor who is incompatible with his intended recipient donates an organ to a compatible patient on the waiting list for cadaveric organs, in exchange for a priority allocation of a cadaveric organ to the donor's intended recipient. Thus, two transplantations can be performed in circumstances that would otherwise have permitted neither.

By using paired kidney exchange, the recipient benefits from the known advantages of living donation. Furthermore, paired kidney exchange reduces the duration of dialysis before transplantation and expands the pool of living donors. In countries where living donors are the main source of organs, cross-over transplantation should be developed as a method of increasing the number of transplants. The kidney exchange programme should be promoted as offering a solution to the need for a transplant where otherwise there would be no organs available.

2.3.3.2 Medical leave for organ donation
Currently, organ donors risk a loss of wages or even loss of employment because of the time away from work that is required for donation (4). In many countries, there is legislation that provides 30-day paid medical leave for all employees who donate an organ for transplantation (5). No one should have to incur a personal expense for donating an organ.

2.3.3.3 Ensuring access to organ for previous donors
The health and well being of living donors should be monitored in a follow-up register in order to document medical problems associated with donation that occur over the ensuing years (6). The need for a transplant in a previous kidney donor should justify a high priority in the allocation of a kidney should the donor subsequently need it.

2.3.3.4 Donor insurance
A national plan should be enacted that provides life and disability insurance for all living donors, including a mechanism to ensure that they do not incur catastrophic medical expenses as a result of their donation.

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2.4   Ethical issues in transplantation

RECOMMENDATIONS ON ETHICS
1.   It is the right of individuals to donate as well as to receive an organ (level of evidence: B).
2.   Commercially motivated renal transplantation is unacceptable, has been widely prohibited by law, and the International Society of Transplantation strongly opposes its practice (level of evidence: B).
3.   Given the increasing success of living donor transplants as judged by graft and patient survival, and given the scarcity of cadaveric organs, living-donor transplants should be encouraged. The appeal for using living donors in renal transplantation is in part due to the continuing shortage of cadaveric donors (level of evidence: B).
4.   The altruistic living donor must give informed consent, which can only be obtained if he has a proper understanding of the risk involved (e.g., pain, hernia (5%), infection (2%), pneumothorax (5%) and death [1:3000]) (level of evidence: B).
5.   A patient should be treated as an 'end' and not as a 'means'. Respect for dignity, integrity and authenticity of the person is a basic human right (level of evidence: B).
6.   Acceptance of living unrelated donors should be done only after the local ethical committee has given permission or, as required by the country, permission by the Courts (level of evidence: C).
7.   In the last instance, what is and what is not ethical should be determined by the balance between clinical utilitarian demand (saving lives in a cost-effective way) and respect for an individual's right to donate or not to donate an organ in life or after death (level of evidence: C).

2.4.1   *Primary ethical principles*
A number of primary principles are widely accepted as forming the bedrock of medical ethics (1-4). In individual cases, conflict often arises in trying to adhere to all of these principles at the same time.

2.4.1.1   *Beneficence: Doing good*
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.

2.4.1.2   *Non-maleficence: Avoiding harm*
Making sure that the balance between benefit and harm is appropriate is an important clinical judgment.
A high standard of donor assessment and risk limitation is therefore of paramount importance before living kidney donation takes place.

2.4.1.3   *Respect for autonomy*
Patients with the capacity to understand relevant information, to consider its implications, and to come to a communicable decision are deemed to have decision-making capacity. Their decision to donate should therefore be respected.

2.4.1.4   *Justice: Promoting fairness*
The principle of justice is very important in kidney distribution, where demand far outstrips supply. In that context, the allocation of organs requires a ranking system in order of priority, with moral justification for the method by which a patient's ranking is decided. In transplantation, scarce resources usually have to be carefully allocated to recipients chosen from a larger pool of the population.

2.4.2   *Cadaveric organ donation*
There has been an increase in living-donor organ procurement in recent years. The bulk of available organs still come from cadaveric donors, brain-dead donors, along with organs from the NHBD procurement programme now used by a number of transplant centres. However, this resource base is shrinking. This, in combination with the ever-increasing rise in potential recipients, is a cause of considerable pressure on the transplantation programme.

2.4.2.1 Cadaveric organ donor

In most countries, obtaining consent to proceed with organ donation is a major barrier to overcome. 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 a number of European countries, the opposite pertains. Consent is presumed unless the patient has specifically opted out before death. This type of legislation appears to influence organ donation favourably, but may be seen as intruding on the individual's rights.

The greater the experience of the persons asking for relatives' consent, whether they be an intensive care physician, neurosurgeon, transplant coordinator or social worker, the greater the chance that consent will be given. Intensivists who discuss brain death and the consequences with a patient's family should always be able to answer their questions on organ donation. Furthermore, many clinicians experience discomfort in approaching relatives and discussing the concept of brain death, and any perceived awkwardness on their part may adversely influence relatives. Educational programmes (such as the European Donor Hospital Education Programme [EDHEP]) greatly aid intensivists in increasing awareness and improving skills in obtaining permission for donation from bereaved relatives. In some countries hospital authorities have attempted to bypass this reluctance by enforcing a 'required request' or 'routine inquiry'.

2.4.2.2 Allocation of cadaveric organs

Who 'owns' cadaveric organs and who makes the decision regarding allocation are both issues in need of clarification (5). However, there is a general presumption that the State holds the responsibility for allocation or disposal of the organs, which it discharges by delegation to the appropriate transplant team (6).

To date, the notion that cadaveric donation and allocation can be made conditional upon personal attributes, e.g., race, religion or wealth of the recipient, is not an accepted premise. European systems that involve attempts at welfare maximization and utility are generally acceptable and maximize benefits by distributing kidneys on the basis of (HLA) matching in kidney transplantation. These allocation systems (e.g., Euro-transplant, UK Transplant) allocate points to recipients to add priority for long waiting time, matchability, and sensitization. All such kidney distribution systems should be transparent and regularly audited.

2.4.3 Living organ donors

The ethical approach to organ donation is conditioned principally by those rules that seek to be charitable while preserving autonomy.

Given the increasing success of living donor transplant, as judged by graft and patient survival, and given the scarcity of cadaveric organs, living-donor transplant has hitherto been regarded as a regrettable necessity (8); but the chronic shortage of cadaver organs has recently caused a more general acceptance of living-donor transplants. The results are better than cadaver grafts, the donor's autonomy is respected, and the act is recognized as emotionally fulfilling for donors as well as recipients.

2.4.3.1 Payment of altruistic donors

The cornerstone of clinical transplantation has been the altruistic donation of kidneys from living relatives. Societies which support the development of transplantation have generally refused to assign a monetary value to a transplantable organ or tissue: the gift of a transplant is therefore priceless, and legal control now exists in European countries to prevent payments for living related organs.

The World Health Organization 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.

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2.5 Policies to increase the number of cadaveric donors

Throughout Europe, the gap is increasing between the 'supply of' and 'demand for' kidney transplants. There are, however, three interesting exceptions: Spain, Austria and Belgium. In these countries, kidney donation exceeds 40 kidneys per million population. According to current registry data in those countries, this is sufficient to plateau the kidney transplant waiting lists, and in the case of Spain, to produce a decrease (1). Elsewhere in Europe, cadaveric kidney donation rates have been static or have declined since 1989. Table 4 lists the kidney transplant rates in 2001 for various European countries.

Table 4: Kidney transplant rates in 2001

Country	Cadaveric kidneys (pmp)	Living-donor kidneys (pmp)	Total kidneys (pmp)
Spain	46.1	0.5	46.7
France	32	1.7	33.7
Republic of Ireland	32.6	0.5	33.1
Italy	25	1.7	26.7
UK	19	6.1	25.1
Scandia Transplant	28.6	10.4	39
Euro Transplant	32	5.1	37.1

During the 1990s, there was a spate of papers, mostly from individual countries and registries, which examined the ways in which the number of kidney donors could be increased locally from rates of 6-10 per million population (pmp) per year up to 20-25 pmp. The data suggests this could be successfully achieved and almost certainly exceeded. Most studies examined single initiatives, such as changing the transplant law, rather than the development of integrated donor programmes. The act of donation is a complex phenomenon depending on many factors and interactions, few of which individually have been proven useful or generally applicable throughout the European Community. Well-designed studies are needed urgently. A donation is the result of a chain of events, the final result of which will depend upon its weakest link.

Even when the individual links have been strengthened, each element of the process of donation must be integrated into the operational policies developed in tune with national moral and cultural values.

For a guideline document on kidney transplantation such as this, it is fairly easy to set a minimum standard to which countries should aspire. It is another matter to recommend specific, donor-promoting activities for which individual countries and professional organizations should aim. Nevertheless, it is possible to include some options, which are described below.

2.5.1 Approach 1: Increase the supply of transplants from living donors

The USA and Norway have substantially 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. It is likely that laparoscopic donor nephrectomy (less time off work, shorter hospital stay) has helped recruit living donors in the USA.

Although living-donor rates are now increasing in Europe, rates could be further improved at different stages in the referral process:

*   Nephrologists, at non-transplanting as well as transplanting centres, should be encouraged to discuss openly the subject of living donation with families of patients suffering end-stage renal disease, preferably before the patient begins dialysis. This results in pre-dialysis transplantation, increased transplant rates and a more efficient use of dialysis resources.
*   Counselling facilities (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.
*   Each transplant centre should work to an approved screening protocol, such that the predicted mortality risk of living donation does not exceed 1 in 3000 (6).
*   If legally permitted, living unrelated donors should be encouraged.

RECOMMENDATIONS

1. Authorities and health professionals should increase public awareness of the option for donating a kidney to a family member and the resulting benefits.
2. All nephrologists involved in caring for ESRD patients should be aware of the need to explore the donor option early with the family when a patient presents with early-stage renal disease.
3. 'Living donor co-ordinators' should be appointed to transplant units to integrate and oversee the exhaustive process of donor selection and health checks within a family.

2.5.1.1 Living unrelated kidney donation

In many countries in Europe, altruistic non-consanguineous kidney donation is allowed legally, provided that checks are made for altruistic motivation and exclusion, as far as possible, of the possibility of organ sale (2). An exception is the UK, where unrelated donation is only legally possible with approval by a statutory body, the Unrelated Living Donor Regulatory Authority, to which all non-consanguineous donor offers must be referred for prior ratification.

> **RECOMMENDATION**
> Living related and unrelated donation should be encouraged, within national laws.

2.5.1.2 'Non-directed' living-donor transplantation

'Non-directed' living-donor transplantation between altruistic donor and a recipient unknown to the donor is possible and is being developed in a few centres in the USA (3). Though controversional, there seems no moral or social reason to exclude such donors. However, there are ethical and legal concerns about this type of donation which at the moment make it difficult to include in a recommendation list.

2.5.1.3 Payment to living donors from central organization

Should donors be paid money to donate kidneys to a central organization, which will then match the kidney with a suitable recipient?

> **RECOMMENDATION**
> Legislation in every European country currently forbids payment for organs.

2.5.2 Approach 2: Increase supply and use of cadaveric kidneys

2.5.2.1 Donor cards

In many countries, publicity schemes encourage the population to carry donor cards, or to register their wish to donate (opting-in) on a computerized donor register. In the UK, 8 million individuals are now registered on the 'opting-in' computer, while 5-10% of the population prefer carrying donor cards. Yet no more than 50 donors per year result from these initiatives. For such schemes to succeed, continuous publicity is essential to increase opted-in donors and transplant centres. Intensive care physicians and transplant co-ordinators should be mandated to access the register routinely to identify the wishes of potential cadaveric donors.

> **RECOMMENDATION (LEVEL OF EVIDENCE: C)**
> In all countries without presumed consent law, further efforts should be made to recruit donors through an opting-in register or by carrying cards.

2.5.2.2 Improved organization and resources

Services must be more organized and better resourced to increase cadaver donation. In several countries (e.g., UK, Czech Republic), the number of intensive care beds is probably too low currently to achieve more than 20 donors pmp from intensive-care patients. In high-donating countries with better resourced intensive care units (e.g., Spain, Belgium), the staff responsible for donation (transplant co-ordinators) have been expanded and given proper financial support. Furthermore, there are successful education programmes, such as EDHEP or institutional audits such as Donor Action, which have increased and maintained the awareness of intensive care physicians of the need for cadaver donation, and to help them deal with the emotional stress involved in approaching the donor families to discuss donation. Transplant co-ordinators are also given the responsibility of public relations, with the aim of avoiding adverse media publicity, and liaising with coroners.

> **RECOMMENDATION (LEVEL OF EVIDENCE: C)**
> Professional organizations, within countries, should, where necessary, maintain pressure on Government Health Departments to maintain an adequate number of intensive care beds; to create a cadre of national transplant co-ordinators; to fund and deploy educational programmes for intensive care physicians, such as EDHEP; and encourage initiatives such as Donor Action.

2.5.2.3 'Opting-out' legislation

The introduction of opting-out legislation appears, based on the data available, to be associated with increased rates of cadaveric donation. In Europe, the four countries which have exceeded 20 kidney donors pmp per annum (Spain, Austria, Belgium and the Czech Republic) all have opting-out legislation. Adverse publicity led to a softening of the practice, with a consequent decrease in donation rates. Other countries with presumed consent law practise 'soft' presumed consent, in which the family's views are taken into account. In contrast,

countries with informed consent generally do not perform as well, the main exception being the USA, where kidney donation rates now exceed 25 donors pmp.

> **RECOMMENDATION**
> For these guidelines it is not possible to make a recommendation about something as fundamental as changing the law on cadaver donation.

2.5.2.4   Criteria for donor suitability
Non-heart-beating donors (NHBDs): Before brain death guidelines were introduced in 1976, NHBDs produced a high frequency of primary non-function and were abandoned as a source of kidneys for transplant. Recently, in-situ perfusion of recently dead bodies has been developed in the UK and Holland with encouraging results. Kidneys may be put onto a continuous perfusion machine and their viability assessed using flow measurements and urinary enzyme excretion (4) and presumed consent leglslation would allow many more NHBDs; rapid intra-arterial cold perfusion of a recently deceased person should be allowed before family members arrive at the hospital in the vast majority of cases. Where informed consent law operates however, perfusion without relatives' permission is technically an unwarranted assault. Agreement by the coroner (the legal custodian of forensic evidence in accidental death) could allow perfusion without permission. The practice of NHBD could then expand significantly.

> **RECOMMENDATION (LEVEL OF EVIDENCE: B)**
> Greater use should be made of NHBDs. Transplant staff should create policies for recently dead admissions to casualty departments to be used as NHBDs. Local coroners should be consulted regarding the legal implications.

2.5.2.5   Elderly donors
Although the long-term survival of kidneys from elderly donors (over 60 years) is 10-15% less than those taken from younger donors, better results may be obtained with carefully selected older donors and shortening of the cold ischaemic time (5).

> **RECOMMENDATION**
> The use of careful selected donors over 60 should be maintained and encouraged as a continuing source of cadaveric kidneys.

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2.6   Kidney donor selection and refusal criteria

RECOMMENDATIONS FOR SELECTION AND REFUSAL CRITERIA FOR CADAVER
HEART-BEATING KIDNEY DONORS

1.   Any brain dead comatose subject should be considered a potential organ donor, without age limits (level of evidence: C).
2.   Consensus for organ harvesting from relatives or significant others should be obtained according to local law and policies for obtaining consent. Individuals who objected to donation during life must always be excluded (level of evidence: C).
3.   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 criteria, and sometimes unsafe sexual behavior within the prior 2 months, if these activities can be ascertained or are suspected (level of evidence: B).
4.   A good-quality organ must be guaranteed to the recipient 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 (level of evidence: B).

2.6.1   Discussion

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.

Today, age limits for organ donation are not fixed. Traditionally, subjects older than 55 years were considered unsuitable, but the worldwide scarcity of transplantable organs has led to the use of cadaveric donors older than those accepted previously. 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. However, long-term graft survival is less (1). In addition, the main physiological risk factor affecting 'older' kidneys is a long cold ischaemia time (2,3). In keeping with these observations, the modern definition of a suitable donor has less restrictive age requirements, and more emphasis is placed on the physical condition of the donor, and specifically of the organ to be donated, with the aim of reducing the possibility of discarding a usable organ. Thus, there are now no absolute age limits to donation. However, since older donors present more comorbidity, in addition to careful selection, a short ischaemia time is also necessary. The same trend towards extending the upper age donation limit to over 55 years also applies to living donors (4).

RECOMMENDATION

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.

2.6.2   Infections

The potential donor must be checked for HIV-1 and -2, 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, infections of unknown aetiology, family history of (or clinical signs that may be caused by) Creutzfeldt-Jacob disease, and active syphilis.

The risk of HIV transmission to organ recipients is high from potential donors for whom intravenous drug use is suspected. Moreover, serology tests during the incubation period of HIV (2 months) or hepatitis (up to 6 months) may be negative. In addition, the serology of potential donors could be altered if they have received large amounts of fluids during resuscitation manoeuvres to control massive blood loss (5). In this situation, unacceptable donors may appear to have normal serology due to dilution effects, and serological tests must therefore be repeated.

2.6.3   Special exceptions for infections

HCV-positive donor: In an HCV-positive recipient, transplant is allowed following informed consent. In a HCV-negative recipient, such a transplant is risky; however, in emergency situations, following informed consent by the recipient, it may be possible.

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 anti-HBsAg antibody titre ≥ 10 mIU/mL, transplant is allowed after informed consent. In an HBsAg-negative recipient with undetectable anti-HbsAg antibody, transplant is allowed only for life-saving situations, when HDV antigen is negative and following informed consent.

HBc-antibody-positive donor: In liver transplantation, the risk of transmitting hepatitis B from an HBcAg-positive donor to the recipient is high (50%). 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-HBsAg antibody titre ≥ 10 mIU/mL, following consent. In an HBsAg-negative recipient with no anti-HBsAg antibody, only life-saving transplants are allowed, after informed consent.

2.6.4   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. For example, the serum level of human chorionic gonadotrophin (hCG) must be measured to exclude choriocarcinoma in suspect donors.

With other cancers, if less than 10 years have elapsed since completion of treatment, only life-saving transplants are recommended. Successful renal transplants have been performed with kidneys affected by small, low grade renal carcinomas, which were completely excised. Such recipients require very careful follow-up (6).

2.6.5   Special exceptions for malignant tumours

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 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.

Donors affected by the following low-grade (grades 1 and 2) brain tumours are suitable for kidney donation (7):
• 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 recipients affected by the following high-grade (grades 3 and 4) tumours are suitable for transplantation 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.

Patients affected by brain tumours of any grade who have undergone ventriculo-peritoneal shunting must be excluded due to the high risk of systemic dissemination of tumour cells through the shunt.

2.6.6   Vascular condition and renal function

Important risk factors in organ failure are a prolonged history of diabetes mellitus or serious hypertension with retinal vascular damage. Previous myocardial infarction, coronary bypass and angina, severe systemic vascular disease, events of long-lasting hypotension, oliguria, or a long-lasting intensive care stay are parameters for excluding a potential donor or for considering him to be a single- rather than a multi-organ donor. According to the aforementioned general criteria for potential donors, careful evaluation of their kidney function is required.

There is general agreement for evaluating a donor's renal function using creatinine clearance calculated according to the Cockcroft-Gault formula, which corrects the serum creatinine value for age, body weight and sex (8). In addition, the condition of the urinary tract can be assessed by 24-h proteinuria and ultrasound kidney imaging. These parameters are also valid in screening elderly donors. In many transplant centres, a calculated creatinine clearance level of 260 ml/min is at the lower range of normal for kidneys that are usable for two recipients, independent of the histology of the organ. Instead, other centres recommend a biopsy to evaluate arteriolar narrowing and arteriolar sclerosis according to the Karpinsky criteria (9), when the level of creatinine clearance is less than 100 ml/min (Table 5).

Table 5: Semi-quantitative scale for renal biopsy scoring (Karpinski et al.,1999)

	Score
Glomerular score	
No globally sclerosed glomeruli	0
< 20% global glomerulosclerosis	1
20-50% global glomerulosclerosis	2
> 50% global glomerulosclerosis	3
Interstitial score	
Absent glomeri	0
< 20% of cortical parenchyma replaced by fibrous connective tissue	1
20-50% of cortical parenchyma replaced by fibrous connective tissue	2
> 50% of cortical parenchyma replaced by fibrous connective tissue	3
Tubular score	
Absent tubules	0
< 20% of tubules affected	1
20-50% of tubules affected	2
> 50% of tubules affected	3
Vascular score	
Arteriolar narrowing (or hyaline arteriolosclerosis)[a]	
absent	0
increased wall thickness but to a degree that is less than de diameter of the lumen	1
wall thickness that is equal or slightly greater than de diameter of the lumen	2
wall thickness that far exceeds the diameter of the lumen, with extreme luminal narrowing or occlusion	3
Arterial sclerosis (or intimal fibrous thickening –fibroplasia) [a]	
Absent	0
increased wall thickness but to a degree that is less than de diameter of the lumen	1
wall thickness that is equal or slightly greater than de diameter of the lumen	2
wall thickness that far exceeds the diameter of the lumen, with extreme luminal narrowing or occlusion	3

[a]For the vascular lesions, both arterioles and arteries are evaluated separately. However, for the vascular score, the most severe lesion of either arterioles or arteries determines the final grade.

2.6.7   Marginal donors

Everywhere, the number of patients awaiting kidney transplantation has grown and their average age has increased (10). In addition, the average cadaveric donor is older than in the past due to a decrease in deaths from traumatic causes. In Spain, the percentage of donors over the age of 60 was 27% between 1992 and 1997 (11), while in the USA, 44% of donors were over the age of 50 in 1997 (12). In the past, these older candidates would not have been considered as kidney donors because of the increased risk for graft non-function or delayed function (13). But in the present circumstances of a scarcity of kidneys for transplantation, the definition of an acceptable donor kidney has been enlarged (14,15).

Currently, the criteria that define this so-called 'marginal donor' kidney have not been standardized. It is therefore necessary to re-evaluate parameters of acceptability for organs that would otherwise not be considered for transplantation. Parameters are decided according to the transplant results that a given centre wishes to achieve (16). They usually include:
- Age
- Diabetes mellitus
- Hypertension
- Serious vascular disease
- Serum creatinine
- Proteinuria
- Kidney weight
- Renal histology evaluated by biopsy.

As noted, a long, cold ischaemia time easily produces a delayed post-transplant renal functionality in these suboptimal grafts. This, in turn, is a negative prognostic index of lasting normal graft function. However, rejection episodes are rarer with older kidneys than with younger ones. Since marginal kidney transplants have a significant survival benefit when compared with maintenance dialysis (17), and since long-term results are worse, with short-term results being more satisfactory, it is therefore logical to utilize older kidneys for older recipients (18). This is particularly indicated in regional transplant programmes 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 programmes. Patients over 60 years old should be offered the possibility of a graft from a marginal donor. They must then confirm their acceptance of a less-than-optimal organ and even an eventual double graft.

The following parameters need to be considered in a marginal organ (19):
- 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; in this situation, the organs are still valuable for single graft.
- Calculated creatinine clearance of less than 50 mL/min; in this situation, the organs should be used as dual graft or discarded if histologically abnormal.
- Approximately 5-20% of glomerulosclerosis shown in biopsy with at least 25 glomeruli taken from both kidneys; in this situation, the organs are still valuable for a single or double graft.
- More than 20% glomerulosclerosis; in this situation, the organs should be discarded.

The real clinical meaning of each of the above criteria is not clear because its rigorous statistical validation with multivariate analysis has not been performed. For example, opinions regarding the value of pre-transplant renal biopsy are still divergent (20, 21).

2.6.8   One graft or two grafts per recipient

The rationale for developing a programme of dual marginal kidney transplantation, or alternatively for not doing so, is based on two conflicting concepts. On one hand, it is argued that kidneys with a small nephron mass undergo hyperfiltration and glomerular hypertension which causes progressive glomerulosclerosis (22). A single marginal kidney has a reduced renal mass and a suboptimal number of nephrons that will be further reduced by cold ischaemia time, transplant trauma, and the nephrotoxicity of immunosuppressive therapy. To increase nephron mass and prevent the above mentioned kidney damage, simultaneous transplantation of both kidneys to the same recipient in this case might be a solution. On the other hand, it is argued that marginal kidneys have some functional reserve that can only be verified after transplantation. Indeed, often the glomerular filtration rate increases after renal transplantation (23-25). Therefore it is argued that dual transplantation is redundant.

Considering these two opposing hypotheses, in the light of current knowledge; kidneys that are judged unsuitable based on functional or histological aspects should either both be transplanted into a single recipient or should be discarded (26).

To date, the surgical technique for dual renal grafting has not been standardized (27).

Preliminary data for double kidney age-matched recipients show fewer rejection episodes when

compared with younger recipients of single kidneys (28), while a prospective multicentre study by Remuzzi et al. (29) concludes that double-kidney transplants are safe, well tolerated and result in no more surgical complications than single-graft operations. Nevertheless, the evidence concerning dual-kidney transplantation indicates that there should be more prospective studies with a longer period of follow-up. Researchers should aim to determine which kidneys might be suitable for dual transplantation. At present, the only general consensus is for kidneys considered by everyone to be unsuitable for transplant. The principal disagreement is over which indicators reliably identify those kidneys suitable for dual transplantation.

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3.   KIDNEY RECIPIENT

3.1   Pre-transplant therapy

3.1.1   Abnormal urogenital tract

RECOMMENDATIONS (LEVEL OF EVIDENCE: B/C)
- 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: vertebral/vascular anomalies, anal atresia, tracheo-oesophageal fistula, oesophageal atresia, 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 (1,2).
- 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, supravesical urinary diversion is crucial (2,3-6). 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 (1).

3.1.2   Urinary diversion
In patients with absent bladder (e.g., cystectomy for bladder cancer) or sphincter insufficiency (e.g., neurogenic, iatrogenic), supravesical urinary diversions must be performed, such as conduits or continent catheterizable pouches with umbilical stoma. In low-compliance bladders with intact sphincters, both bladder augmentation and continent pouches with umbilical stoma are successful alternatives (2,4-6); intermittent catheterization is more comfortable via an umbilical stoma than via the urethra.

Most authors prefer a supravesical urinary diversion to be performed at least 10-12 weeks before transplantation (2,5,6). At the same time, chronically infected kidneys or bladders can be removed. Nevertheless, bladder augmentation is possible post transplant as well (3,5). Complications arise mainly from the urinary diversions, such as stenosis of ureteral anastomosis or stoma stenosis or insufficiency (3,5,6). Patients with conduits, augmented or abnormal bladders have an increased risk of urinary infection with the danger of transplant loss (1,2,4,5), and antibiotic prophylaxis is therefore recommended during the first 6 months post transplant (2).

3.1.3   Indications for pre-transplant nephrectomy

3.1.3.1   Autosomal dominant polycystic kidney disease (ADPKD)
In ADPKD, uni- or bilateral nephrectomy is necessary when there is insufficient space for the transplant kidney, or due to complications, such as cyst infection, cyst rupture with/without haematuria, pain or abdominal girth. The kidney removal can be done either by one-stage nephrectomy with concomitant renal grafting, or as a two-stage procedure. Both procedures have similar complication rates and outcomes for transplantation (7).

3.1.3.2 Medically refractory hypertension
In medically refractory hypertension, bilateral nephrectomy leads to reduction in the number of antihypertensive medications in most patients. Dorsal lumbotomy has less morbidity than midline incision (8).

3.1.3.3 Chronically infected kidneys or renal or urothelial cancer
Other indications for pre-transplant/nephrectomy are chronically infected kidneys or kidneys in which renal or urothelial cancer is suspected.

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3.2   Selection and refusal criteria

> **RECOMMENDATIONS (LEVEL OF EVIDENCE: B)**
> A distinct preoperative cardiovascular work up of all transplant candidates is mandatory to improve organ and patient survival in the post-transplant period.

Kidney transplantation should be considered as the first therapeutic choice for all suitable patients with endstage renal disease due to diabetes mellitus.

3.2.1   Comorbidity
Comorbid conditions, such as diabetes mellitus or cardiovascular disease, are known to have a major impact on the morbidity and mortality of kidney transplant patients (2,11). Death with a functioning kidney allograft has been shown to occur in no less than 42% of kidney-transplanted patients (9), with cardiac death being the most important cause. It is therefore of great importance to evaluate carefully potential transplant recipients. In particular, a distinct cardiovascular work-up of transplant candidates should be performed to reduce early graft failure due to technical problems and to improve patient survival in the post-transplant period (6).

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

3.2.2 Cardiovascular disease

3.2.2.1 Cardiac disease
Since dialysis patients have an excessive risk of cardiovascular disease, a careful work-up has to be performed in every kidney transplant candidate (8). 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 suspicious case, especially in elderly and diabetic dialysis patients. Revascularization, either surgical or by coronary angioplasty, should be performed in every suitable transplant candidate (3).

3.2.2.2 Peripheral artery disease
Peripheral artery 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 amputation (6).

Duplex sonography of the peripheral arteries and radiography of the pelvis should be done routinely before transplantation. In any cases of doubt, especially in diabetic patients, angiography or non-invasive imaging of the pelvic and peripheral arterial vessels with computed tomography (CT) or magnetic resonance tomography (MRT) are strongly recommended.

Severe vascular occlusive disease of the carotid has to be excluded by duplex sonography to avoid intra- or post-operative stroke (1).

3.2.2.3 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 (5). Furthermore, isolated kidney transplantation, or combined kidney-pancreas transplantation, reduces the long-term morbidity and mortality of uraemic diabetic patients when compared to dialysis.

Thus, kidney transplantation should be considered in every diabetic uraemic patient who has no other severe contraindication, especially cardiovascular disease. Since the incidence of cardiovascular disease in diabetic dialysis patients is exceptionally high, coronary and peripheral angiography or non-invasive imaging procedures (e.g., MRT-angiography) are necessary in most cases to exclude patients with a high vascular risk (10). Bladder neuropathy is a frequent complication in diabetic patients, and it is recommended that a urological work-up should be performed, including uroflow with measurement of residual urine. In severe cases of diabetic uropathy it is rational to perform an additional urodynamic examination.

3.2.3 Age
Although there is no controversy about the fact that kidney transplantation offers improved survival and quality of life in younger patients with end-stage renal failure, an ongoing debate exists about kidney transplantation in the elderly. Reduced mortality in transplanted patients compared to patients on the waiting list aged over 65 years has been shown (7). 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. It is advisable to enrol elderly transplant patients in the senior programme of EUROTRANSPLANT as well as apply for living-donor transplantation.

In elderly dialysis patients selected for kidney transplantation, special attention must be paid to concomitant cardiovascular disease and possible pre-existing cancer. If a careful work-up of the patient excludes severe cardiovascular or cancer disease, it is our opinion that kidney transplantation can be performed in patients older than 65 years with good results.

An increased risk for post-transplant infections in the elderly has been shown and has to be considered in the selection of eligible patients.

3.2.4 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. Despite this fact, however, the recurrence rate should be discussed thoroughly with patients. Living donation should be critically discussed in diseases with early and very high recurrence rates. 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 6 lists the recurrence rates of the most important diseases.

Table 6: 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 (cyclosphosphamide, high-dose 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[1] 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[2] + vasculitis	~17 %	?	Cyclophosphamide, steroid boluses

[1] *ACE inhibitor = angiotensin-converting enzyme inhibitor*
[2] *ANCA = antineutrophil cytoplasmic antibody*

3.2.5   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 potential transplant candidates should be seen by an ear, nose and throat specialist, dentist, dermatologist, urologist and gynaecologist to rule out infectious foci. Other infections screened prior to transplantation are HBV, HCV, tuberculosis, cytomegalovirus, and *Treponema pallidum*.

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. The incidence of HBV in dialysis patients has decreased significantly in the last decade. Thus, it is not surprising that the incidence of HBV-positive patients on the waiting list is currently very low.

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.

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3.3   Transplantation in pregnancy

3.3.1   Graft survival

Chronic renal failure is frequently associated with sexual dysfunction and infertility. After successful kidney transplantation, an improvement in sexual life and fertility is observed, and counselling about the possibility of a pregnancy is mandatory for both male and female patients. During pregnancy, a transplant recipient's renal function may be impaired in 10-15% of cases, but there is not necessarily a connection between the reduction of functionality and the pregnancy (1). Moreover, in studies on the long-term graft prognosis of pregnant patients compared to the general transplanted population, all but one of five authors, have demonstrated that pregnancy appears to have no effect on graft survival (2-6).

The incidence of abortion, spontaneous (14%) or therapeutic (20%), in transplanted women is similar to that of the general population. However, compared to the general population, they have respectively greater rates (50%) of pre-term delivery and their offspring have a 20% chance of lower birthweight (7).

Pregnancies in transplanted women are often unproblematic. Nonetheless, such patients should always be considered to be at high risk. Their care requires careful co-operation between the obstetrician, nephrologist and urologist.

RECOMMENDATIONS

After kidney transplantation, pregnancy is possible and well tolerated for most patients with normal graft function and no, or well-controlled, hypertension. However, pregnant transplanted women must be considered always to be at high risk and their care requires the co-operation of the obstetrician, nephrologist and urologist (level of evidence: B).

3.3.2 Planning pregnancy

Ideally, pregnancy should be planned at a moment of good general and graft health. Usually the ideal moment for pregnancy is not earlier or later than 1-2 years from the kidney transplantation. Earlier pregnancy is not suggested because the compliance of the host to the graft may need some months to reach equilibrium (8). Meanwhile, a pregnancy occurring several years after transplantation, when some chronic rejection and/or some deterioration of renal function may have developed, is also not recommended. However, sporadic successful pregnancies have occurred outside the ideal period.

Scientific data show no significant difference in outcome between early, recommended, or late pregnancies if graft function and immunosuppressive therapy are stabilized and if there is no sign of rejection, hypertension, proteinuria, hydronephrosis or chronic infection. If these conditions are satisfied, then any time can be good for a pregnancy.

It should be noted that the presence of hydronephrosis during pregnancy increases the risk of infection and lithiasis, and may worsen in the last trimester.

It is important that pregnancy is detected as soon as possible so that monitoring and adjustment of immunosuppressive therapy can begin as soon as possible.

> **RECOMMENDATIONS**
> Pregnancy should be planned at a moment of good general and graft health, when renal function and immunosuppressive therapy are stabilized and there is no sign of rejection, hypertension, proteinuria, hydronephrosis or chronic infection (level of evidence: B).

3.3.3 Immunosuppressive treatment

The immunosuppressive treatment usually administered during pregnancy is cyclosporine, with or without azathioprine and prednisone (9). These drugs pass through the placental barrier but apparently do not increase the risk of teratogenicity. Blood levels of cyclosporine may change, and usually decrease, especially during the third trimester. This is due to increased volume distribution and pharmacokinesis. Its dosage should usually be augmented (9). A few recent papers have suggested that the new drug, tacrolimus (10-12), used in kidney, heart and liver transplantation, may also be safe in pregnancy. However, there are only sporadic reports on the effects of MMF, which is contraindicated, as is, sirolimus.

> **RECOMMENDATIONS**
> Cyclosporine and tacrolimus apparently do not increase the risk of teratogenicity and they are currently used with or without steroids and azathioprine. Treatment with mycophenolate mofetil or sirolimus is not recommended (level of evidence: C).

3.3.4 Controls

Controls on pregnant transplanted patients should focus on:
* Hypertension
* Proteinuria
* Renal function
* Rejection
* Infection.

Hypertension affects a high percentage of patients with renal transplant. If it begins prior to 28 weeks' gestation, the incidences of stillbirth, low birth weight and fetal death increase (13). Pre-eclampsia occurs in almost 30% of transplanted pregnant women; when it is associated with hypertension, pre-term delivery is possible.

Proteinuria is abnormally present in 30-40% of pregnancies in the last trimester. The presence of proteinuria in the first few months, or its association with hypertension, chronic rejection or glomerulonephritis, is an unfavourable fetal prognostic factor.

It cannot be demonstrated that pregnancy affects the function of a good kidney transplant. However, some authors have reported that reduced renal function prior to pregnancy may show a progressive deterioration over 2 years until dialysis becomes necessary (14). A subtle impairment of renal function during gestation may mask a progressive chronic subclinical rejection, but graft function may also be impaired by the noxious effect of hyperfiltration exacerbated during pregnancy (7). However, it has not been proven that glomerulosclerosis can be caused by an increased glomerular filtration rate.

The frequency of rejection is no higher than that expected for non-pregnant transplant patients and is unusual when the graft is stabilized. The diagnosis of rejection may be difficult and may require renal biopsy.

Bacterial urinary tract infection should be prevented by frequent urine cultures. Viral infections can be transmitted to the offspring; in the case of CMV infection, this may present as mental retardation. Culture of the amniotic fluid will reveal any fetal infection (15).

> **RECOMMENDATIONS**
> Controls should focus on hypertension (pre-eclampsia affects 30% of patients), proteinuria, renal function, rejection and infection (level of evidence: B).

3.3.5   Follow-up
Abortion rates are high, for both medical and personal reasons. Although a vaginal delivery is not mechanically impaired by the abdominal graft, a high rate of Caesarian section (50%) is observed. Breastfeeding is not suggested because of the potential risk to the child 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.

There is very little literature on the growth and long-term medical outcome of children born to a kidney-transplanted mother, including their adult life. As noted above, the offspring are often born prematurely and have a reduced birth weight. In addition, there is a 3-5% risk of a structural malformation of a generally random typology. Studies on the long-term effects of fetal exposure to immunosuppressive therapy are only just beginning. No other important data exist at present.

Children of fathers in immunosuppressive treatment following kidney transplantation are clinically no different from those of the general population. They are less frequently aborted than fetuses of kidney transplanted mothers. However, if the father is affected by hereditary disease, there is a higher risk of transmission.

> **RECOMMENDATIONS**
> Although vaginal delivery is possible, the rate of Caesarian section is high (50%). Breastfeeding is not suggested because of the potential risk to the child of ingesting immunosuppressive agents (level of evidence: C).

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4.   TRANSPLANTATION TECHNIQUES

4.1   Kidney transplantation

4.1.1   Transplant preparation
•   Prepare the back table with on a sterile iced bed at +4°C.

4.1.1.1   Kidney
•   Remove the perirenal fat.
•   The renal fat should be kept in place around the hilum and the ureter.
•   Check for the absence of renal tumours.
•   Rinse the kidney with +4°C serum via the renal artery.

4.1.1.2   Vein
•   The right kidney should be removed, with the infra renal caudal vena cava for lengthening the renal vein, on the back table (1,3,14,17).
•   Collaterals ligature.

4.1.1.3   Artery
•   Preserve the aortic patch.
•   In case of atheroma in the ostium, remove the aortic patch.
•   In case of multiple arteries without patch, repair on the back table for reducing the duration of the vascular anastomosis (4,8,35).

4.1.1.4   Ureter
•   Check for double ureter.

- Keep the peri-pyelic and peri-ureteral fat in place, which includes the ureteral vessels.

4.1.2 Technique in adults

4.1.2.1 Approach
- Extraperitoneal approach of one fossa iliac.
- Transplantation in the contralateral fossa iliac is preferable, as this means that the renal pelvis and ureter are superficial and are not being compressed.
- Exact lymphostasis with clips or ligatures to avoid lymphocele is mandatory.

4.1.2.2 Vascular anastomosis
- The vein is implanted onto the external iliac vein.
- The artery is implanted onto the external (or common) iliac artery. Try to avoid atheromatous plaques.
- Check to see that the vessels to be transplanted are in a good position in the recipient.
- Both anastomoses are preformed with two halves of running non-absorbable monofile sutures 5 x 0 or 6 x 0.
- The internal iliac artery should be kept in place, in case it is compromised it may cause erectile dysfunction (21).

4.1.2.3 Ureter anastomosis
- Ureterovesical extravesical implantation at the anterior surface of the bladder dome according to the antirefluxive Lich-Gregoir technique is the method of choice (22).
- The ureter is sutured to the bladder mucosa by two halves of running absorbable 5 x 0 sutures. This technique gives better results than open implantation to the bladder (i.e., Leadbetter-Politano ureteroneocystostomy) (43,45).
- A double stent, 16 cm, 6F or 7F, may be placed to facilitate and protect the anastomosis. It is strongly recommended in cases of tricky anastomosis, e.g., as in paediatric transplant. Several transplant groups have used a double stent routinely (6,7,34,36,46). The stent must be removed 4-6 weeks after the transplantation.
- The uretero-ureteral anastomosis will not be used except in particular circumstances, when the aim is to preserve the ureter in case of surgical complication or for a third transplantation.

4.1.3 Special cases

4.1.3.1 Kidneys taken from children of less than 15 kg in bodyweight
En-bloc transplantation should be performed, including:
- The proximal aorta is closed by a suture, with its distal part re-implanted in the external iliac artery.
- The distal part of the inferior vena cava is closed by overstitching and its proximal part is anastomosed onto the external iliac vein.
- An alternative method is to insert the aorta of the donor in the external iliac artery (if the vessels are congruent) and to patch the inferior vena cava on the external iliac vein.
- The two ureters are anastomosed in double pant with a single tunnel in the bladder, according to the Lich-Gregoir procedure.

4.1.3.2 Depending on the vascular state of the recipient
If the iliac arteries do not allow clamping:
- Do an endarteriectomy of all iliac axes and fix the intima by U-shape sutures before performing the anastomosis.
- If an endarteriectomy is impossible, make a bridge with an artery which comes from the same donor or with a prosthesis in which the kidney can be re-implanted (38).
- If a prosthetic replacement has been previously carried out, re-implant the renal artery in the prosthesis by resecting out a small piece of the prosthetic wall (20).
- If a normal inferior vena cava is not available due to anomaly or thrombosis, one gonadic vein or the original renal vein of the recipient can be used for venous anastomosis.

4.1.3.3 Paediatric recipient
The disproportionate gap between the size of the transplant organ and the size of the child recipient can pose particular problems. Large kidneys must be placed in a higher position towards the lumbar fossa, with the renal artery being anastomosed to the aorta and the renal vein to the inferior vena cava of the recipient. In general, however, fossa iliac can also be used for transplantation in children (18,26).

4.1.4. Early complications

4.1.4.1 Wall abscesses
These are more frequent when the recipients are obese or old (27). They can be prevented by using:
- Prophylactic antibiotic therapy.
- Subcutaneous aspirative drainage in obese patients.
- Careful closure of the subcutaneous layer.

4.1.4.2 Urinary fistulae
Urinary fistulae are the most common early complication. They occur in 3-5% of cases in which no double J-stent has been used. They can occur on the ureter, bladder, or on a calyx:
- On the ureter, the most frequent cause is necrosis of the ureter because of ischaemia, viral infection (BK, CMV) (24), rejection or by dehiscence of the anastomosis.
- On the bladder, it is due to a closure that is not water-tight.
- On the calyx, it is due to necrosis by ligature of a polar artery (39).

Treatment: With regards to treatment, ureteral fistulae can be treated by open surgery or by the percutaneous method.
- Open surgery - re-open the transplant incision. The ureter is re-cut and a double J-stented uretero-ureteral anastomosis is made using the patient's original ureter (10,19).
- Percutaneous treatment - in cases where it is possible to localize the fistula, it is worth trying nephrostomy and/or vesical catheter and double J-stent.
- Vesical fistulae can be treated by suprapubic or transurethral catheter. Calyceal fistulae are treated by nephrostomy or vesical catheter and double J-stent. If this fails, polar nephrectomy can be tried (23).

> **RECOMMENDATIONS**
> 1. Use a short ureter and keep the peri-ureteral fat around the hilus and ureteral vessels (41).
> 2. Avoid ligature of an inferior polar artery because of the risk of parenchymal necrosis and fistulae.
> 3. Put in place a prophylactic double J-stent and a vesical catheter.

4.1.4.3 Arterial thrombosis
The risk of arterial thrombosis is 0.5% in the first post-operative week. Risk factors include:
- Intimal rupture or poor suture technique.
- Vascular resistance is too high.
- Paediatric transplants.

Treatment: This should be aggressive, i.e., surgical re-intervention in cases of thrombosis on the kidney transplant because the kidney transplant can be vascularized by venous retrograde flow. A radiological thrombectomy may be done in the first 12 hours with success.

> **RECOMMENDATIONS**
> 1. Preserve the aortic patch.
> 2. Look for intimal rupture before anastomosing the kidney.
> 3. Avoid plicature of the artery.
> 4. In the absence of an aortic patch, make a large anastomosis onto the external iliac artery, which should be opened up with a punch perforator in order to have a large arterial opening.

4.1.4.4 Venal thrombosis
Venous thrombosis is a rare occurrence, occurring in 0.5% of kidney transplants. With aggressive treatment, i.e., thrombectomy, the chances of success are very poor, but treatment is successful in rare cases. More often, patients are treated with transplantectomy.

> **RECOMMENDATIONS**
> 1. On the right, lengthen the renal vein with the infra renal vena cava in order to avoid an anastomosis under tension.
> 2. Carry out a large venous anastomosis; at declamping, if the renal vein is tight, re-do the venous anastomosis.

4.1.5. Late complications

4.1.5.1 Ureteral stenosis
The renal calices and pelvis are dilated and there is often an elevated creatinine level. These stenoses occur in 5% of transplants, and can present late, between 1 and 10 years post transplant (29). There are three causes of ureteral stenosis:

1.   Ureter dilatation due to vesical high pressure with thickened bladder wall or urinary retention.
2.   Vesicorenal reflux.
3.   Ureterovesical stenosis due to scar formation and/or bed surgical technique. They comprise 80% of ureteral stenoses.

Treatment: This can be endoscopic, either transurethral or percutaneous. The outcome of the dilatations is better when the stenosis occurs early and distally (2,5,28,37,42). Treatment can also be with open surgery using a uretero-ureteral anastomosis to the patient's ureter or a vesicopyelostomy. Stasis during pregnancy should be treated with percutaneous nephrostomy or a temporary double J-catheter.

RECOMMENDATIONS
1.   Use a short and well-vascularized ureter, surrounded by peri-ureteral fat.
2.   Do not stenose the anastomosis during the last part of the muscular suture.
3.   Use a double J-stent to reduce the frequency of ureteral stenosis.

4.1.5.2 Reflux and acute pyelonephritis
- Acute pyelonephritis is a rare complication, with reflux being more common.
- Reflux in the renal cavity is found in up to 30% of cases after Leadbetter and in 80% after Lich-Gregoir, if the submucous tunnel is short, and 10% of cases if it is long.
- In lower urinary tract infections, the risk of acute pyelonephritis is 80% in the presence of reflux, and 10% without reflux (31,32).

Treatment: Reflux complicated by acute pyelonephritis should be treated with:
- An uretero-ureteral anastomosis if the native ureter is not refluxive.

Or:
- An uretero-vesical re-implantation with a long tunnel if the original ureter is refluxive or unusable.

RECOMMENDATIONS
1.   The submucous tunnel for the uretero-vesical anastomosis should be 3-4 cm long.
2.   Avoid lower urinary tract infections.

4.1.5.3 Kidney stones
Kidney stones can be a concern in transplantation, and may be transplanted with the kidney or acquired. The risk of kidney stones is less than 1% of transplants (30). The stones manifest themselves by haematuria or obstruction (11). There are several treatment options:
- Some stones are eliminated spontaneously.
- In an emergency, if the stones are obstructing or producing anuria, a double J-catheter should be put in place by the retrograde method, or by percutaneous nephrostomy using ultrasound.
- Calyceal and smaller renal stones should be removed by extracorporeal shockwave lithotripsy (ESWL).
- Lager calyceal or pyelonephric stones should be removed by percutaneous or open nephrolithotomy (13,16,25).
- Ureterolithiasis should be treated by ESWL or ureteroscopy (9,12).

RECOMMENDATIONS
1.   Treat hyperparathyroidism in the recipient.
2.   Use re-absorbable threads for the urinary anastomosis.
3.   Treat urinary obstructions and infections.

4.1.5.4 Renal artery stenosis
Renal artery stenosis has a frequency of 10%. It is diagnosed by Doppler sonography and arteriography, which show the presence of the stenosis in cases of arterial hypertension and/or increased creatinine. Treatment options include the following:
- Interventional treatment is not always necessary. Many patients respond well to medical treatment and some stenoses may regress.

- The indication for interventional treatment depends on the degree of the stenosis. Intervention is indicated if the stenosis is > 70%.
- Transluminal dilatations give poorer results than surgical incisions, but their simplicity makes them the first-line treatment for aligned and distal stenosis (33).
- Open surgery is reserved for plicature or anastomotic stenosis, and involves resection with direct implantation. Repair with the saphenous vein must be avoided.

RECOMMENDATIONS
1. Remove an arterial patch from the donor and use it for the transplant (17).
2. Examine the artery intima, fix the intima, or re-cut the artery, in case of lesions.
3. Position the kidney before carrying out the anastomosis. If the kidney is to be transplanted into the iliac fossa in a low position, use a vein that is 1-2 cm longer than the artery, keep a left renal vein long, and lengthen the renal vein of the right kidney with the vena cava to avoid arterial bending - the artery must be straight.
4. Avoid anastomoses which are too tight, and cut out a small piece of the arterial wall for re-implantation.

4.1.5.5 Arterio-venous fistulae or arterio-calyceal fistulae after renal biopsy
These are seen in 10% of cases. They usually regress spontaneously, but when persistent, embolization should be used.

RECOMMENDATION
Avoid very deep biopsy reaching the renal hilus.

4.1.5.6 Lymphocele
This occurs secondary to insufficient lymphostasis of the iliac vessels or lymph secretion of the transplant kidney.

Treatment: No treatment is necessary for mild lymphocele, where there is no compression of the iliac vessels or ureter. If treatment is needed, marsupialization with epiploplasty can be performed, either as open surgery or by laparoscopy (15,40,44).

RECOMMENDATION
Strict lymphostasis should be maintained by clips or ligatures of the lymphatic vessels.

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4.2 Kidney transplantation in abnormal urogenital tract

RECOMMENDATIONS (LEVEL OF EVIDENCE: B/C)

1. The technique used to implant transplant ureters in augmentations or conduits is the same as the method used with a patient's own ureters, e.g., following cystectomy for bladder cancer (Bricker, Wallace). In bladder augmentations or continent pouches, the ureters are implanted by tunnel technique (Goodwin-Hohenfellner), or (as favoured in most patients) extravesically, using, for example, Lich-Gregoir, Matthisen, or Leadbetter methods (1,2).

2. In ureterocystoplasty, it is feasible to perform uretero-ureterostomy with one of the patient's own ureters (1).

3. 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).

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5. MATCHING OF DONORS AND RECIPIENTS

> **RECOMMENDATION (LEVEL OF EVIDENCE: A AND B)**
> The ABO blood group and the HLA-A,-B and -DR phenotypes should be ascertained for all candidates awaiting kidney transplantation.

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

5.1 Histocompatibility (HLA) matching

Histocompatibility (HLA) matching is of considerable importance in kidney transplantation (4).
Transplant outcome correlates with the number of HLA mismatches. Transplant mismatching leads to proliferation and activation of the recipient patient'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 a remarkable polymorphism (3). 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.

5.1.1 Practical aspects of HLA-testing (1)
- Laboratories who co-operate with a transplant centre for HLA-testing and cross matching in organ transplantation must meet high-quality criteria (accreditation standards) to ensure accuracy and reliability.
- Cells for HLA-typing should be obtained from recipient's peripheral blood (with an appropriate anticoagulant (e.g., ethylene diamine tetra-acetic acid (EDTA) or acid-citrate-dextrose [ACD]).
- Comprehensive sets of reagents capable of detecting all commonly occurring HLA antigens in the relevant ethnic group must be used.
- DNA typing techniques are nowadays widely used. Reporting of HLA antigens should conform to the latest WHO nomenclature (5).

5.2 Cross matching

To avoid hyper-acute rejection of kidney transplant T-cells, a cross match test must be performed before each kidney transplantation. The cross match test detects preformed HLA-allo-antibodies in the serum of the recipient directed against lymphocytes of the potential donor. Routinely, a lymphocytotoxicity assay is used (detection of complement-dependent 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. These antibodies are not relevant in acute rejection because, in most cases, they are non-HLA antibodies. Inactivation of IgM antibodies by serum treatment with dithiothreitol (DTT) and incubation at 37°C can minimize false-positive cross match results.

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 (1).

5.3 Pre-existing HLA-specific antibodies

Circulating anti-HLA antibodies have to be regularly checked for in transplant recipients (every 3 months) (2). Pre-existing HLA-antibodies in potential transplant recipients may be due to blood transfusions, previously performed organ transplantations, or prior pregnancies. The results of HLA-antibody testing in a recipient's serum are expressed as percentage panel reactivity antibody (%PRA) and as the HLA specificity that they react against.

In the standard complement-dependent lymphocytotoxicity (CDC) assay, the panel of lymphocytes used are selected to cover most of the common HLA-alleles in the donor population. As in the widely used cytotoxicity assay, there is a low sensitivity to detect anti-class II antibodies, while non-complement fixing antibodies (e.g., IgG2) are not detected at all. Thus, alternative, more specific and sensitive assays have been developed for HLA-antibody testing (e.g., flow cytometry and enzyme-linked immunoabsorbent assay (ELISA)-based methods).

In highly sensitized (PRA > 80%) patients on the transplant waiting list, a careful analysis of HLA antibody specificities 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.

5.4 ABO blood group matching

The matching of ABO blood group antigens is of critical importance in kidney transplantation. 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. However, in order to avoid an increasing imbalance between demand and supply in cadaveric kidney transplantation in O recipients, ABO identity is mandatory.

In living donor transplantation, ABO compatibility is as acceptable as ABO identity.

5.5 Viral disease

> **RECOMMENDATION (LEVEL OF EVIDENCE: B AND C)**
> Testing of CMV infection status is necessary to define the risk of developing CMV disease in the recipient and to plan prophylactic treatment.

5.5.1 Cytomegalovirus (CMV)

Cytomegalovirus infection is the most common viral disease after a kidney transplantation. It may have severe clinical consequences in terms of recipient morbidity and mortality and graft survival. There is a clear association between CMV infection and acute rejection episodes.

Cytomegalovirus infection status must be evaluated, using IgG antibody testing with ELISA, in both donor and recipient prior to kidney transplantation. This allows the risk of CMV disease to be defined in the recipient and to plan prophylactic treatment regimens if necessary.

In CMV IgG antibody-negative recipients who have received a transplant from a CMV-positive donor, there is a very high risk of primary CMV infection, which is usually detected after 4-5 weeks post transplant. Thus, in these recipients, adequate prophylaxis with gangcyclovir is strongly recommended.

Secondary CMV infection can be found in CMV antibody-positive recipients either due to a re-activation of latent virus infection or re-infection by a new strain of CMV.

5.5.2 Hepatitis B (HBV) and hepatitis C (HCV) infection

Potential donors with hepatitis B surface antigen (HBsAg) must be excluded from organ donation. 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.

Hepatitis C-positive patients should be monitored closely after kidney transplantation. Viral replication (HCV RNA) and liver enzymes should be monitored on a regularly basis. If possible, reduction of immunosuppresion may be beneficial for the long-term hepatic outcome of these patients. 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.

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6. IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION

RECOMMENDATIONS

1. 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.
2. 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).
3. There is no firm clinical evidence that steroids may be safely dropped from macrolide-based immunosuppression, though they may be safely stopped after 6 months in patients who have not suffered acute rejection. Mycophenolate mofetil has virtually replaced azathioprine, having a superior efficacy and acceptable therapeutic index, and most importantly, being non-nephrotoxic. In suitable patients, both cyclosporine and prednisolone dosage may be reduced (or steroids stopped) in patients receiving MMF and cyclosporine. Bone marrow function should be regularly monitored in patients receiving MMF.
4. 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. Nevertheless, the availability of five reasonably safe, efficacious agents greatly increases the practitioners ability to 'tailor' regimens to a patient's individual need.
5. The use of polyclonal or monoclonal anti-T-cell biological induction therapies is not without risk, particularly in patients who are not naturally immune to EBV or CMV. This therapy should not be routinely used in a low-risk first-transplant recipient. If such induction therapy is used, the risks of viral disease and cancer must be explained to the patient beforehand.
6. High-affinity humanized or chimeric monoclonal antibodies (daclizumab, basiliximab) are expensive, but may safely be given as an induction treatment along with macrolide-based immunosuppressants and are very likely to reduce the frequency of early rejection.

6.1 Introduction

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.

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. However, this has not always been the situation. Until 1962, renal allografts were rejected immediately, or within 6 months, despite large dosages of non-selective immunosuppressives, such as high-dose steroids, whole-body irradiation, or thoracic duct drainage. Between 1962 and 1982, azathioprine (Imuran) and prednisolone provided moderately effective and cheap treatment that resulted in 60% graft survival at 1 year for cadaveric renal transplants.

However, the risk of haemorrhage, sepsis and metabolic problems were high. The discovery of a non-marrow-suppressive T-cell inhibitor, cyclosporine A, brought in a new era of safer, more effective, immunosuppression for transplant recipients. Two pivotal trials in 1979-1983 provided unequivocal evidence that cyclosporine treatment could result in substantially better kidney transplant survival at 3 years compared with azathioprine-based treatment. More importantly, the therapeutic index of cyclosporine-based regimens was better, since it was possible to reduce the prednisolone dosage, and thus bone marrow toxicity was largely avoidable. Both cyclosporine, and the other commonly used macrolide and calcineurin-inhibitor, tacrolimus, have significant side-effects, which are hazardous to the graft and the patient. Cyclosporine is nephrotoxic in the majority of patients, and its long-term use may be a cause of recent in chronic allograft nephropathy. It also causes hypercholesterolaemia, hypertension, gum hypertrophy, hirsuitsm and acne. Tacrolimus is a more powerful immunosuppressive, but is associated with diabetes, neurological and electrolyte abnormalities, and nephrotoxicity (though to a lesser extent than cyclosporine). Nonetheless, the vast majority of renal transplant practitioners between 1983 and 1995 eagerly embraced cyclosporine because of its superior efficacy and lack of bone marrow toxicity. The 'cyclosporine era' resulted in an exemplary improvement in kidney graft survival, and has led the way to success in pancreas, heart, liver, and lung transplantation.

Current policies now aim at achieving acceptable 10-year graft survival, and the pharmaceutical industry has been restless in its search for non-nephrotoxic, yet potent, selective immunosuppressants for transplantation. Newcomers include mycophenolate mofetil (MMF) (CellCept), an 'engineered' drug, based on mycophenalic acid, a drug used in the 1970s for rheumatoid arthritis. It acts by inhibiting inosine monophosphate dehydrogenase, and thus the rate of synthesis of guanosine monophosphate in the de-novo purine pathway, upon which lymphocytes depend for function and proliferation. It is non-nephrotoxic; however, in large doses (> 2 g per day), it inhibits bone marrow function and may cause diarrhoea in up to 15% of patients. Its co-administration with prednisolone and cyclosporine or tacrolimus has allowed the reduction of the dose of these compounds, and at the same time a reduction in the rejection rate. The new immunosuppressive sirolimus (Rapamune) suppresses lymphocyte proliferation and differentiation. It inhibits both calcium-dependent and calcium-independent pathways and blocks cytokine signals to proliferation of T-cells. Similar effects are seen on B-cells. It has been shown to be effective when combined with cyclosporine in the prevention of rejection, but exhibits the dose-dependent side-effects of thrombocytopenia and hypercholesterolaemia. The data on graft and patient survival on these recently developed drugs is available for up to 3 years from prospective randomized studies. Cyclosporine and tacrolimus have now been effectively documented with regard to long-term efficacy and safety. Sirolimus is being more widely used but is not yet licenced in Europe for routine prescription.

Prophylactic immunosuppression in the 1980s, particularly in the USA, featured the emergence of 'induction' treatments, using biological agents, including antithymocyte globulin (ATG), and after renal transplantation. These therapies have the advantage of allowing cyclosporine to be stopped during the 10 days of recovery of the graft from ischaemic injury, following which triple therapy was started on cessation of the reduction course. Triple therapy was originally based on cyclosporine, azathioprine and prednisolone, with more recently MMF being substituted for azathioprine. Graft-rejection rates were generally lower with induction treatment; however, there is no evidence of better long-term graft survival in patients receiving induction therapy versus those who have not. The risks of post-operative viral infection and cancer (post-transplant lymphoproliferative disease) have increased in susceptible patients given induction therapy compared to those who were not. Since 1997, polyclonal (ATG) or monoclonal (OKT3) induction has tended to be replaced by high-affinity anti-IL-2 receptor monoclonal antibodies (daclizumab and basiliximab). These agents are given in a short course during the post-transplantation period, are safe, and have been shown in randomized controlled trials to reduce the prevalence of acute cellular rejection by approximately 50% (13,14).

6.2   Primary immunosuppressive prophylaxis

6.2.1   Cyclosporine A
Modern therapy is based on cyclosporine A, used together with more recent drugs, such as MMF instead of azathioprine. Prednisolone is still regarded by the majority of practitioners as a fundamental adjunct to primary immunosuppression, although prednisolone withdrawal has been possible. Two prospective randomized studies demonstrated in the early 1980s that cyclosporine-based therapy gave superior graft survival 3 years

after transplantation. The first from Canada (Canadian Multicentre Trial Group 1983) compared cyclosporine plus triple therapy, with or without ALG/ATG induction, with the same treatment but without cyclosporine. In 1983, the European Multi-Centre Trial Group published the results of a controlled, randomized trial of cyclosporine monotherapy versus azathioprine and prednisolone treatment. In both trials, relatively high doses (20 mg/day) of cyclosporine were used, given as Sandimmune (cyclosporine powder given in a capsule). For the first 5 years of both trials, cyclosporine blood level monitoring was not performed. There was a very high percentage of drug withdrawals for cyclosporine toxicity, approximately 80% in both studies. The results regarding patient survival in each group are shown in Table 7 (1,2).

The improved graft survival rate calculated on the basis of 'intention to treat' (10% at 3 years in the Canadian study, and 22% at 3 years in the European study), with no increased mortality in either trial attributable to cyclosporine, was very encouraging. However, in both studies, the graft-survival curves ultimately converged after approximately 10 years. In retrospect, it seems likely that that the majority of these late graft failures in the experimental groups were due to cyclosporine toxicity, or early conversion of patients from experimental to controlled groups.

Cyclosporine A micro-emulsion (Neoral) gives a better pharmacokinetic profile and appears to be more acceptable to patients. More importantly, the area under the absorption curve was higher with Neoral than with Sandimmune. This enabled reduction of cyclosporine dose without sacrificing efficacy, a finding confirmed by a randomized, controlled trial in 1997 (3). Neoral treatment was also found to be associated with a reduced rejection rate 1 year after transplantation, with 1-year rates of 34% for Neoral and 47% for Sandimmune (4).

6.2.2 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 overdosing, leading to nephrotoxicity, and under-dosing, which may lead to rejection. Tacrolimus and cyclosporine have been compared in prospective, randomized studies (see table) (5, 6). In Pirsch et al. (5), the Sandimmune form of cyclosporine was used, with virtually equal graft- and patient-survival rates in both treatment groups up to 3 years. However, tacrolimus is associated with prevalence for diabetes of 20% compared with 4% for cyclosporine.

The 5 years' survival data from this trial (15) (intention-to-treat analysis) indicate persistent equivalence of graft and patient survival in each arm of the study. The incidences of treatment failure were significantly lower in the tacrolimus group (43.8%) versus cyclosporine (56.3% p=0.008). Crossover between each arm of the study for graft rejection or adverse event was significantly higher in patients randomized to cyclosporine (27.5%) than in those receiving tacrolimus (9.3%); p<0.001. Overall graft survival at 5 years was equivalent in each group, although hypercholesterolaemia and serum creatinine >150umol/l was more common in the cyclosporine arm (17.4% and 62.0%, respectively) than in the tacrolimus arm (4.7%, p=0.0008) and 40.4% (p=0.0017), respectively.

The second comparative study of tacrolimus versus cyclosporine (6) also used the Sandimmune form of cyclosporine A. Mayer et al. (6) reported a reduction in the incidence of transplant rejection associated with tacrolimus, but similar graft- and patient-survival rates in both groups. Micro-emulsion-based cyclosporine (Neoral) (which is now the universally available form of cyclosporine) has recently been compared in a study with tacrolimus (7), the results of which are also summarized in Table 7. In this small single-centre study, it appears that cyclosporine Neoral compares favourably with tacrolimus at least with regard to an improved rejection rate at 1 year.

6.2.3 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 (8-11). In the European trial (8), MMF was added to cyclosporine and steroids at doses of 2 g/day and 3 g/day. Both dosages considerably reduced graft-rejection rates at 1 year, with 17% and 14% for 2 g and 3 g MMF, respectively, versus 46% for the placebo group.

Similar results were reported in the US study (9), in which the doses of MMF were also 2 g and 3g/day, added to cyclosporine and steroids and ATG-induction therapy, and compared with cyclosporine, prednisolone and azathioprine. However, at 3 years, patient- and graft-survival rates were not significantly different in any of the three groups in the European study. In the Tricontinental Study (10), in which MMF was substituted for azathioprine at 2 g and 3 g/day, with cyclosporine and prednisolone in all three groups, the incidence of acute rejection was 20% and 16% for MMF, 2 g and 3 g/day, respectively, versus 35% for the control (azathioprine) group. A comparison of the incidences of acute rejection in the placebo group in the European study (8) versus the azathioprine group in the Tricontinental Study (10) showed no statistically significance difference. Since

cyclosporine and steroids were given to both groups of patients, and selection criteria were similar though geographically separate, it might be concluded that Imuran therapy has lost its traditional place in modern immunosuppressive regimens. Indeed, MMF is now routinely used as a primary- or second-line therapy in place of azathioprine in many units. Nowadays, azathioprine is usually reserved only for those patients who cannot tolerate MMF.

In a retrospective study of 66,000 patients on the US renal data system, a comparison of the 4-year graft survival in azathioprine-treated versus MMF-treated patients was done. Mycophenolate mofetil decreased the relative rate for chronic allograft rejection by 27% compared with azathioprine, an effect independent of the reduction of acute cellular rejection in patients receiving MMF. Patient survival was the same in both azathioprine- and MMF-treated groups (12).

Recently published data indicates that co-administration of MMF with cyclosporine, with or without prednisolone, allows a reduction or cessation of macrolide dosage (16). A multicentre randomised control trial of 187 renal transplant patients receiving triple therapy (cyclosporine, MMF 2 g/day and steroids) compared creatinine clearance, rejection rate and serum cholesterol 6 months after stopping cyclosporine in the experimental group. Eight mild and 1 severe rejections occurred after cyclosporine withdrawal all of which were reversed, compared to 2 episodes in the control group (p=0.03). Excluding those cases of rejection, mean creatinine clearance was higher in those who stopped cyclosporine (+7.5mL/min, p=0.02). In the intention-to-treat population, cyclosporine withdrawal was associated with a lower total serum cholesterol and low-density lipoprotein (p=0.015). It is to be hoped that macrolide-reducing regimens will result in a reduction of chronic allograft nephropathy.

6.2.4   *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 agent for rejection, has been found to act synergistically with, and be equipotent to, cyclosporine. It shows dose-dependent, reversible thrombocytopenia and hypercholesterolaemia (17). The first large multi-centre randomized controlled trial compared sirolimus (Rapamune) with azathioprine in cyclosporine - treated renal transplant recipients (18): although rejection frequency and severity were reduced, renal function was better at 1 year in the azathioprine-treated group, an effect which appeared independent of blood cyclosporine levels. A smaller randomized controlled trial of sirolimus versus cyclosporine for primary suppression (each group receiving azathioprine and steroids) revealed similar rejection rates in both groups, but better renal function at 1 year in the sirolimus-treated patients (19). A similar trial (20) compared sirolimus with cyclosporine in patients also receiving MMF. Rejection rates were not significantly different in either group and serum creatinine was significantly lower in those patients receiving sirolimus.

A large international randomized controlled trial (17) studied efficacy and safety of cyclosporine withdrawal at 3 months from a cyclosporine plus sirolimus maintenance regimen, compared with non-withdrawal: although acute rejection was significantly more frequent after cyclosporine withdrawal (9.8% vs 4.2% p=0.035), renal function and blood pressure were improved in this group and more viral infections were seen in the control patients. A small single-centre randomized controlled trial (21) has shown that primary immunosuppression using basilixmab plus MMF plus sirolimus provided outcomes of renal transplantation similar to a cyclosporine- based regimen. In all these controlled trials, graft survival, mortality and infection rates were approximately equal in cyclosporine and sirolimus-based regimens up to 1 year post transplant. 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 CAR will be a long-term result of its use.

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Table 7: Randomized controlled studies of cyclosporin A

REF	REGIMEN EXP	CONTROL	n	ACR EXP	ACR CONTROL	GRAFT SURVIVAL EXP	GRAFT SURVIVAL CONTROL	PATIENT SURVIVAL EXP	PATIENT SURVIVAL CONTROL	COMPLICATIONS
1 (Canadian multi-centre study 1983)	CyA 20 mg/kg/day and Imuran & Steroid	Imuran & Steroid	103/110			*69% (3 years)	58%	90%	86%	Higher creatinine in Exp. group
2 (European multi-centre study 1983)	CyA 20 mg monotherapy	Imuran & Steroid	117/115			*67% (3 years)	49%	90%	83%	Higher creatinine in Exp. group
5 (Pirsch et al. 1997)	Tacrolimus + Imuran + Steroid	CyA & Im & Pred	205/207	*31%	46%	91% (3 years)	88%	96%	97%	Tacrolimus associated with 20% diabetes
6 (Mayer et al. 1997)	Tac & Im & Pred	CyA & Im & Pred	303/145	*26%	46%	82% (3 years)	86%	93%	96%	
7 (Morris-Stiff et al. 1998)	CyA Neoral & Im & Pred	Tac & Im & Pred	40/40	33%	40%	-	-	-	-	

*P< 0.05. ACR = acute cellular rejection; CyA = cyclosporine A; Exp = experimental; Im = Imuran; Pred = prednisolone.

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# 7.	COMPLICATIONS

## 7.1	Immunological complications

> **RECOMMENDATION**
> 1.	ABO incompatibility should always be avoided between the donor and recipient.
> 2.	A panel-reactive antibody (PRA) profile should be performed on every waiting-list patient.
>	Where national kidney sharing programmes exist, the PRA profile should be included with patient's details, suitable for rapid access when a potential donor becomes available.

*7.1.1	Introduction*

Immunological 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 (1), 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. This is now rare due to donor-recipient ABO matching and the development of routine pre-transplant cross matching between donor cells and recipient serum.
- 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.
- 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 (2).

As discussed below, 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 8), and form the basis for deciding prognosis and treatment.

Table 8: Pathological classification of renal allograft lesions (3)

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.

7.1.2   Hyper-acute rejection (HAR)
This is the most dramatic and destructive immunological attack on the graft. 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 the majority of 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.

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

7.1.2.2   Treatment
Hyper-acute rejection is treated by graft nephrectomy.

7.1.2.3   Prevention
Hyper-acute rejection can be prevented by the avoidance of an ABO-incompatible renal transplant. All patients registered for renal transplantation should have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, transplant rejection, and blood transfusions. Sensitization is increased following renal transplant rejection, if the rejected allograft is removed and immunosuppression stopped (5). Highly sensitized patients (more than 50% PRA) should be considered for favourable prioritization in a points-based matching algorithm (1).

       In a national kidney-sharing programme, identification of the specificity of anti-HLA antibodies in highly sensitized patients, along with crossmatching, allows the detection of acceptable and unacceptable

antigens present in the donor. 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.

7.2 Acute allograft rejection

Acute allograft rejection can be classified into either T-cell mediated (acute cellular rejection, ACR) or antibody-mediated (acute humoral rejection) (Table 9).

> **RECOMMENDATIONS**
> 1. Renal transplant practitioners must be continuously aware of the possibility of acute rejection, particularly during the first 6 months after renal transplantation.
> 2. During hospitalization, daily blood and urine samples should be taken for renal and haematological studies and the patient should be examined.
> 3. There should be a high index of suspicion for rejection in any patient who suffers fever, graft tenderness, or reduced urine output.
> 4. There should be routine access to ultrasound-guided biopsy of the transplant, and there should be sufficient expertize in the hospital pathology department to allow a clear-cut diagnosis of rejection, or other type of allograft dysfunction.
> 5. 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.
> 6. Patients who suffer ACR should be tested as soon as possible for the presence of anti-HLA IgG antibodies reactive with the graft, by CDC cross matching.
> 7. All centres practicing renal transplantation should have access to elective serological profiling of all potential, and actual, waiting-list recipients to define the percentage and specificity of panel reactive antibodies (PRA), and their isotypes, IgG or IgM.
> 8. The laboratory service should also provide a 24-h donor-recipient cross matching service to inform the surgeon of the CDC cross match result expeditiously before a cadaveric renal transplant (within 5 h).

7.2.1   T-cell mediated acute cellular rejection (ACR)

Table 9: T-cell mediated acute cellular rejection

Tubulo-interstitial rejection
- The typical histological hallmarks are infiltration by T-cells, microphages, and to a lesser extent, neutrophils
- The presence of plasma cells is associated with a poorer prognosis (6)

Type II endarteritis
- Histological injury to graft capillaries and small intra-renal vessels is seen in 35-60% of patients with an ACR (7)
- 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) (8)

7.2.1.1   Diagnosis

Patients may develop pain in the graft within the first few months of transplantation, most commonly between 7 days and 3 months. On examination, the patient is pyrexic, and the graft may be enlarged and tender. Urine volumes drop, while there is a fall in creatinine excretion and clearance. Sodium excretion levels fall with the accompanying rise in serum creatinine. Doppler ultrasound scanning of the kidney may show an increased resistance index associated with reduced diastolic flow ('a tight kidney'). The specificity and sensitivity of this test as a non-invasive indicator of rejection have yet to be confirmed.

The gold standard for diagnosis of ACR is renal transplant biopsy, which should be conducted preferably under ultrasound control, using an automated needle biopsy system (e.g., tru-cut, Biopty gun).

7.2.1.2   Treatment

Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously in three, daily, pulses. Anuria, or a steep rise in the serum creatinine thereafter, indicates steroid-refractory rejection, and the need for another 3-day course of pulsed methylprednisolone therapy or anti-T-cell biological agents, such as anti-lymphocyte globulin (ALG) or anti-CD3 monoclonal antibody (OKT3). If biological agents are used, other

immunological suppression should be stopped, and daily T-cell monitoring should be done to minimize the dose of the biological agent.

7.2.2   Antibody mediated (acute humoral rejection)
This can be categorized into capillary or arterial antibody-mediated rejection.
- Capillary (peritubular +/- glomerular): 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 the rejection (9). Humoral rejection is under-diagnosed (10). On biopsy, the appearances are those of oedema and haemorrhage with focal necrosis. Not surprisingly, the prognosis is poorer than when ACR occurs alone. The C4d fraction of complement is present in 100% of cases on histology (10).
- Arterial: In these cases, the injury is more widespread involving larger arteries, which may exhibit fibrinoid necrosis.

7.2.2.1 Diagnosis and treatment
Humoral rejection commonly accompanies ACR and causes the same clinical signs. As in ACR, the diagnosis becomes apparent on renal allograft biopsy. Treatment is undecided.

7.2.3   The cross match
Following the realization that pre-formed anti-HLA cytotoxic antibodies caused rejection (11,12), and with the development of the cross match test (13), HAR has become an extremely uncommon complication. The complement-dependent cytotoxicity test (CDC) is now universally employed in all transplant centres; recipient serum is incubated for 1 h with donor peripheral blood lymphocytes, splenic lymphocytes, or lymph node lymphocytes. IgG makes up the vast majority of damaging anti-HLA antibodies. If these are not excluded by a positive cross match, recipients with IgG antibodies specific for incompatible donor antigen will suffer graft HAR.
        The cross match test can also detect IgM (which may be confirmed by the fluorescent cross match), but these are mainly non-HLA-directed and are non-damaging (14). The dichlorodiphenyltrichloroethane test can routinely discriminate between IgG and IgM, thereby improving the clarity of the cross match result (15).
        Attempts have been made to improve the sensitivity and reliability of the cross match test.
        In summary, the extended CDC test (2h) has not been proven to be beneficial (16). The technique of anti-human globulin augmentation and the use of immuno-magnetic beads have become fashionable in some units, but are still awaiting validation.
        The fluorescent antibody test is more sensitive than CDC, as graft failure is higher in the FAT-positive test, CDC-negative cross match when compared with the FC-negative, CDC-negative cross match (17-20). However, the false-positive and false-negative cross match rate is greater than 15%, and fluorescent-assisted cross matching is still undergoing evaluation (19).

7.3   Chronic allograft rejection (CAR, humoral or unknown pathogenesis)

> **RECOMMENDATIONS**
> 1.   During the years of follow-up after renal transplantation, transplant practitioners must regularly monitor urinary protein secretion, serum creatinine and creatinine clearance.
> 2.   Changes in these parameters over time should trigger hospital admission for renal biopsy.
> 3.   If CAR is confirmed, appropriate medical treatment (e.g., control of hypertension and acidosis, with administration of ACE inhibitors) should be instituted.

7.3.1   Introduction
Twenty-five per cent of patients will lose their grafts due to chronic allograft nephropathy, a sizeable but unknown number of which will have chronic allograft rejection (CAR) (2).
        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. Histological features on biopsy are those of fibrosis, concentric intimal fibroplasia of larger arteries with capillary dilatation, and thickened split basement membranes. Cortical atrophy is advanced and there may be calcification (21).

7.3.2   Diagnosis and treatment
Diagnosis is by renal biopsy. In patients where the diagnosis is made early, there is some evidence (22) that intervention with an ACE inhibitor (e.g., lisinopril), together with oral bicarbonate therapy to prevent acidosis, may reduce the tempo of renal decompensation. However, this is temporizing treatment and, ultimately, the

patient will require another transplant (if fit enough to go on the transplant waiting list), or dialysis therapy. It is likely that CAR is more common in patients who have had early attacks of ACR (23) - a good reason for preventing acute cellular rejection.

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7.5 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 (1) (level of evidence: B). 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.

7.5.1 Prior malignancy in the recipient

This situation can be due to:
- Relapse of a prior neoplasia.
- A latent asymptomatic neoplasia.

7.5.1.1 Relapse of a prior neoplasia

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. If the waiting period is less than 2 years, the risk of relapse is 53%. However, if more than 5 years have elapsed since treatment, the risk is reduced to 13%, while between 2 and 5 years, the risk of relapse is 34%.

For most tumours, the waiting time for transplantation should be 2 years; however, there are some exceptions (2,4,5,7,11,12) (level of evidence: C):

Less than 2 years:
- Basal cell skin cancer.
- Squamous cell carcinoma completely excised.
- Incidentally discovered renal cell carcinoma (RCC).
- In-situ uterine cervical carcinoma.
- Low-grade or in-situ bladder cancer.
- Small single and focal neoplasms.

More than 2 years:
- Symptomatic or large RCC.
- Invasive bladder cancer.
- Prostate cancer.
- Breast carcinoma.
- Malignant melanoma.
- Colorectal carcinoma.
- Invasive uterine cervical carcinoma.

Recurrence rates within the first 2 years have been observed with Wilms' tumour, symptomatic RCC, bladder carcinoma and non-melanoma skin cancer. Although a 5-year waiting period would eliminate the majority of recurrences, this is not practical, especially in older age groups (8). A 2-year waiting period would eliminate 91% of Wilms' tumour recurrences, 64% of bladder cancer recurrences, and 61% of symptomatic RCC recurrences. However, this 2-year waiting period would eliminate only 13% of colorectal recurrences, 19% of breast cancer recurrences, and 40% of prostatic cancer recurrences (3,7,12,15).

The risk of recurrence after kidney transplantation of pre-existing malignancies is given in Table 10.

Table 10: Risk of recurrence of pre-existing malignancies following kidney transplantation

Risk of recurrence
Low risk (0-10%)
• Incidentally discovered RCC
• Lymphomas
• Testicular, uterine, cervical, thyroid cancer
Intermediate risk (10-25%)
• Endometrial cancer
• Wilms' tumour
• Colon, breast and prostate cancer
High risk (> 25%)
• Bladder cancer
• Sarcomas
• Skin cancer
• Symptomatic RCC
• Myelomas

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 (4,11).

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.

7.5.1.2 Latent asymptomatic neoplasia

Patients with end-stage renal disease 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 those older than 50 years, should be screened for the presence of a pre-existing cancer. Evaluation must include:

• 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.
• Chest X-ray.
• Abdominal ultrasound to exclude RCC.

The likelihood of developing acquired cystic kidney disease (ACKD) increases with the duration of dialysis:

• 10-20% (1-3 years)
• 40-60% (3 years)
• 90% (5-10 years).

The prevalence of RCC is 3-4% with ACKD. This rate is 4-100 times greater than the figure described for the general population (0.04%). However, the need to perform renal ultrasound for evaluation of kidney transplantation candidates is controversial. In fact, the American Society of Transplant Physicians does not recommend it because of the frequent regression of ACKD after transplantation.

7.5.2 Transmission of a donor neoplasia to the recipient

Penn has reported more than 250 cases of donor-transmitted cancers. The most common one was RCC, followed by primary lung cancer, malignant melanoma, choriocarcinoma, and breast cancer. Melanoma and choriocarcinoma are the most aggressive donor-transmitted malignancies (75% and 90%, respectively).
A recent report from the United Network for Organ Sharing (UNOS) Transplant Tumor Registry, in the USA, reviewed 650 recipients who had received kidneys from 157 donors with a history of, or active, malignant carcinoma (6,11-13).

Donors with active cancer or prior history of neoplasia should not be considered as possible donors. However, non-melanoma low-grade skin cancer and selected tumours of the central nervous system that have not been subjected to any surgical manipulation may be acceptable, particularly if the donor has a long cancer-free interval prior to organ procurement. The transmission of medulloblastoma, glioma multiforme and malignant glial neoplasm has been reported. The risk of extracranial metastasis is 0.5% for astrocytoma and glioblastoma and 4.5% for medulloblastoma. The risk of transmission increases with intracranial surgery, particularly with ventriculo-atrial or ventriculo-peritoneal shunts. Occasionally, brain metastasis may masquerade as primary brain tumour or cerebral haemorrhage; detection of this circumstance is essential as it is a contraindication for donation.

In selected cases, organs from donors with RCC have been transplanted. This has occurred when the tumour was small and confined to the capsule and there was no evidence of cancer dissemination. In cases of larger or invasive tumours, the recipient will suffer extensive dissemination. In some cases, kidneys with small tumours have been transplanted after tumourectomy. In the case of transplanting a kidney with a non-visualized tumour, graft nephrectomy and suspension of immunosuppression are mandatory.

With other tumours, the risk of transmission is low after 5-10 years without clinical tumour activity. However, Penn described breast and colon cancer transmission after cancer-free intervals of 5 and 8 years.

7.5.3 Development of a new tumour in the recipient after transplantation

The prevalence of cancer after kidney transplantation ranges from 3-26% and it is 4-5 times higher than that of the general population. The Cincinnati Registry in the USA (4,6) observed a total of 9,508 cancers in 8,868 kidney transplant recipients prior to November 1998, in the following distribution:

• Skin cancer, 40%.
• Lymphoproliferative disease, 11%.
• Lung cancer, 5%.
• Renal tumours, 5%.
• Kaposi's sarcoma, 4%.
• Cervical cancer, 4%.
• Vulvar and perineal cancer, 3%.

It is important to note that there has not been an increase in the prevalence of the most common neoplasia of

the general population (lung, breast, prostate and colon). The higher prevalence of cancers in transplant recipients has been related to factors such as:

- Exposure to ultraviolet rays: skin cancer (16).
- Analgesic abuse: urothelial cancer.
- Dialysis-acquired cystic renal disease: renal cancer.
- Immunosuppressors, such as cyclosporine A and anti-CD3 monoclonal antibody (OKT3): impaired immune surveillance.
- Viral infections: EBV, lymphoproliferative disease; herpes 8 virus, Kaposi's sarcoma; human papillomavirus, cervical and anogenital cancer; and HBV or HCV, hepatocarcinoma.
- Chronic antigen immunostimulation.

The presence of an active cancer in the recipient is a contraindication for transplantation due to the increased risk of metastasis and dissemination as a result of immunosuppression therapy.

7.5.4   Annual screening measures
The annual screening measures for detection of a new cancer in a patient in the waiting list include the following.

7.5.4.1   Dermatological examination
Recipients of renal allografts have an increased risk of skin cancer. This cancer represents 40-60% of tumours that develop after kidney transplantation and its prevalence increases with time. The incidence increases with time after kidney transplantation, being 16% at 10 years and 52% at 20 years post transplant. It is closely linked to sun and ultraviolet exposure, to HLA-B27 antigen presence, and to the degree of immunosuppression. An annual dermatological examination and the use of total sun block are recommended for kidney transplant recipients.

7.5.4.2   Nodal examination
The incidence of lymphoproliferative diseases (1-2.5%) has increased since the introduction of cyclosporine, anti-lymphocyte globulin (ALG) and OKT3 (14). They usually present in the first year after transplantation. Most of them are non-Hodgkin lymphomas and B-cell-lymphomas. The treatment requires reduction or suspension of immunosuppressive therapy with a remission rate of 50-68%. Antiviral drugs (acyclovir, ganciclovir) can be useful in some cases.

7.5.4.3   Gynaecological evaluation
Cervical cancer is 3-16 fold higher than in the general population and in 70% corresponds to in-situ carcinoma cervical intraepithelial neoplasia (CIN). Annual colposcopy and cytology are required in transplanted females. Cervical cancer appears to be aetiologically related to infection of the cervix with sexually transmitted oncogenic strains of human papillomavirus (HPV). Increased risk of cervical cancer in transplant recipients is due to either reactivation of latent HPV or deficiency in the immunosuppressed host. The prevalence of HPV in the cervix of transplanted females is almost 45%, though this figure is currently decreasing, as well as CIN prevalence (9). Mammography and gynaecological ultrasound should be periodically performed.

7.5.4.4   Prostate gland evaluation
The prevalence of clinical prostatic adenocarcinoma in the male transplanted population is between 0.3-1.8%. This figure increases with the age of the recipient and can reach 5.8% if PSA screening is performed in males with a renal transplant. All recipients over 50 year of age are required to have an annual PSA and DRE. In addition, PSA levels are not modified by kidney transplantation, and most prostate cancers detected in transplanted patients are clinically localized (84%) at the time of diagnosis (7,10).

7.5.4.5   Faecal occult blood testing
The association of colon cancer with kidney transplantation is much more controversial, although an increased risk factor of 2.6 has been reported. Up to 1998, 386 cases of colorectal cancer have been described in 10,667 transplant recipients. However, it is difficult to define whether or not colonoscopy should be offered as the preferred method of screening, in the absence of other factors implying a high risk of colon cancer development. The usual routine screening test with serum markers (CEA, CA 125, CA 15-3, CA 19-9) is not useful in a transplanted population because of the screening test's low sensitivity and specificity (15).

7.5.4.6   Urinary cytology
The incidence of urothelial tumours is three-fold higher than in the general population. The tumours are usually transitional cell neoplasia, although the incidences of bladder adenocarcinoma and nephrogenic adenoma have also increased. Urinary cytology is mandatory in patients with macro- or micro-haematuria, analgesic

nephropathy, or a prior history of urothelial cancer (2).

7.5.4.7 Renal ultrasound
Renal cell carcinoma usually presents in the patient's own kidneys, but it can be present in the graft.
The prevalence ranges between 0.5-3.9%, which is 10-100-fold higher than in the general population.
The risk factors are:
- ACKD
- previous history of RCC
- Von Hippel Lindau disease
- (perhaps) polycystic kidneys.

Annual ultrasound of the patient's native kidneys and the graft is recommended.

7.5.4.8 Chest X-ray
An annual chest x-ray is recommended.

7.5.5 Conclusion
The risk of cancer is several-fold higher in transplanted patients than in the general population. Cancer is a cause of significant morbidity and mortality in the transplanted population.

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8.   GRAFT AND PATIENT SURVIVAL

RECOMMENDATIONS FOR GRAFT AND PATIENT SURVIVAL (LEVEL OF EVIDENCE: B)
1.   Graft survival following unselected kidney transplantation should be at least 80% after 1 year, 60% after 5 years, and 45% after 10 years (2,4,10,14,18) (Figure 1).
2.   Patient survival following unselected kidney transplantation should be at least 90% after 1 year, 80% after 5 years and 60% after 10 years (2,4,10,14,18).
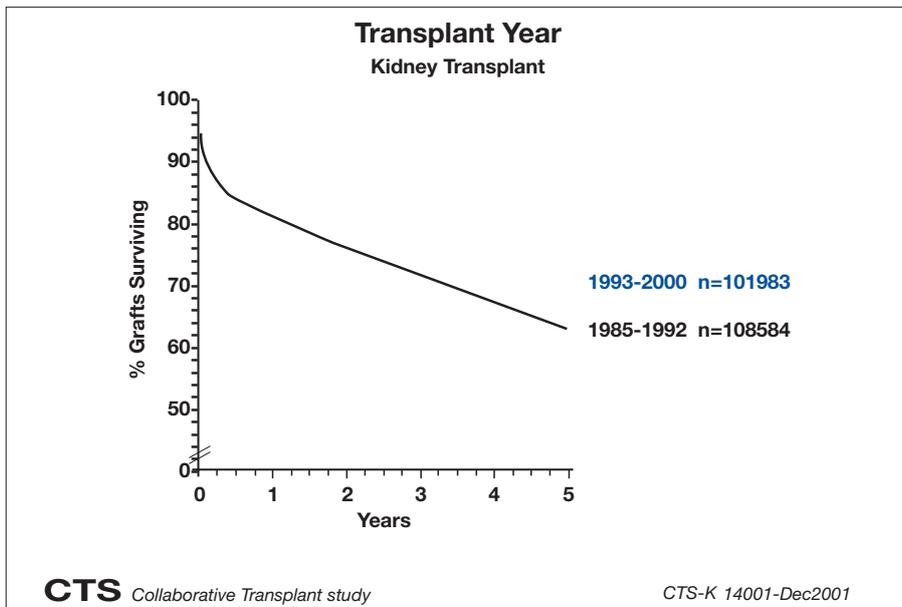
Figure 1: Graft survival following kidney transplantation. (Courtesy of Prof Dr G. Opelz, Heidelberg.)

The above general outcome following kidney transplantation depends on several criteria, which are discussed below.

8.1 Cadaver and living donors

8.1.1 Graft 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 cadaveric 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.

For unrelated living-donor kidney transplantation, graft survival is only slightly dependent on HLA-matching with less than 10% difference between none and six mismatches (Figure 1) (14,15). Husband-to-wife and wife-to-husband transplantations show similar results with 3-year graft survival of 87% if the wife as the recipient has not been pregnant before. In the case of a former pregnancy, the outcome is approximately 10% worse (17).

Five-year graft survival is approximately 84% for siblings, 77% for unselected kidney living donors, and 63-66% for cadaver kidneys (Figure 1) (4). Ten-year graft survival following HLA-identical living donors is 78% for patients with polycystic kidney degeneration and 60% for patients with diabetes (18).

8.1.2 Patient survival
In addition, patient survival following living-donor kidney transplantation is at last 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% (2,4,10,14,15).

8.2 Age of donor and recipient

8.2.1 Donor's age
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. The 5-year graft-survival rate following cadaver-donor transplantation is up to 25% higher for donors aged 18-30 years than for donors older than 70 years (Figure 1) (3,4,13).

Delayed function is also about 20% higher following kidney transplantation of donors older than 65 years compared to donors less then 20 years (4). Particularly noticeable is the influence of donor age in transplantations with six mismatches. In the USA, 5-year graft-survival is 81% for 20-30 year-old donors versus 39% for donors older than 60 years in this group (4,17,18).

Cadaver-kidney transplantation from donors younger than 10 years to recipients older than 20 years, and from donors younger than 6 years to recipients younger than 18 years, has significantly worse graft-survival rates

than kidneys from donors older than 10 years. However, there is no difference in graft-survival rates between kidneys from deceased donors aged between 11 and 40 years. For living donors, the outcome of kidneys from donors older than 65 years is only slightly worse than for kidneys from donors younger than 65 years (Figure 1) (12,14,18).

8.2.2 Recipient's age

In addition, the recipient's age has an important impact on the outcome of transplantation (13). Five-year graft survival in recipients aged 18-50 years is 65%, which is better than 5-year graft survival at 50% in recipients more than 70 years old (Figure 1). In the French transplant network, 1-year graft survival is only 61% for recipients older than 50 years who have been transplanted with kidneys from donors more than 10 years older. In contrast, 3-year graft-survival is 75% in recipients aged 17-45 years, independent of donor age (3).

Nevertheless, the transplantation of kidneys from old donors to old recipients is very feasible with a good success rate. It is not clear yet how important it is to have HLA-matching in this 'old for old' group (19).

8.3   HLA-matching

Both the Collaborative Transplant Study (Figure 1), the HLA Task Force of the Kidney Advisory Group of the United Kingdom Transplant Support Service Authority (UKTSSA) and the United Network for Organ Sharing (UNOS) have clearly demonstrated the impact of HLA-matching on transplantation outcome with an approximately 10% better graft survival, following 0 versus 6 mismatches, both in cadaver and living donors (4,13,14,15).

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 (7). In particular, HLA-DR matching is important with nearly 10% difference in graft survival between 0 and 2 mismatches of HLA-DR (14,15).

8.4   Immunosuppression

Data from the CTS 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 2). The influence of cyclosporine A is especially marked in second kidney transplantation, with about 20% improved 5-year-graft-survival for 1-haplotype-identical related donors (14). As mentioned above, the use of 'modern' immunosuppressive drugs in different combinations has not yet improved the outcome significantly.
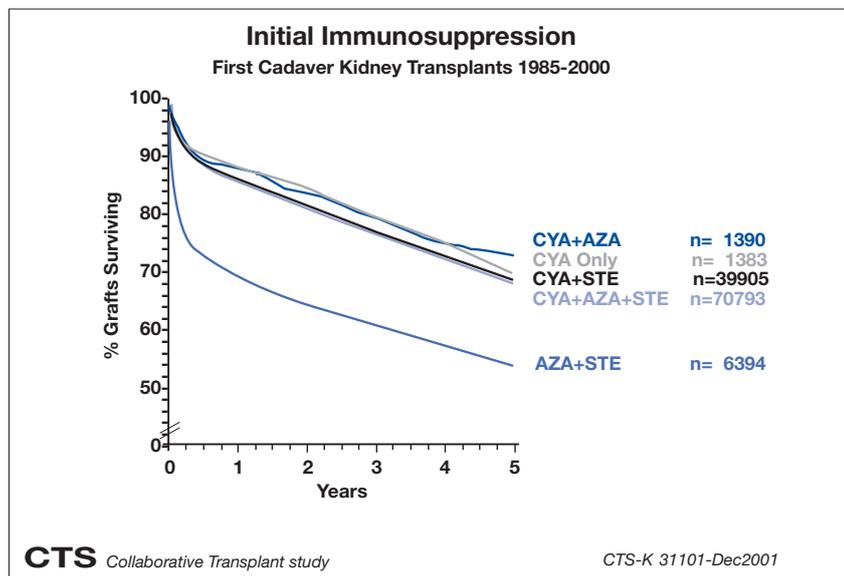

Figure 2: Influence of cyclosporine A-based immunosuppression on graft survival following kidney transplantation. (Courtesy of Prof Dr G. Opelz, Heidelberg.) AZA = azathioprine; CYA = cyclosporine A; STE = steroids.

8.4.1 Number of transplantations

The 5-year graft-survival rate decreases by about 5% from the first to second, second to third, and third to fourth cadaver transplantation. The five-year graft-survival for first cadaver transplantation is 65% versus 58% for second, 52% for third and 45% for fourth or more transplants. For living donors, the worsening of graft function between first and second transplantation is less marked (about 2%), with no, significant, difference between the first and second transplantation of 1-haplotype-identical kidneys (Figure 2) (4).

8.4.2 Cold ischaemia time

The good success of unrelated living-donor kidney transplantation stresses the importance of a short cold ischaemia time. Surprisingly, the shortest ischaemia time of 0-6 h did not have the best outcome in CTS: graft survival was significantly inferior compared to transplantations after 7-12 or 13-24 h of ischaemia. This is because of the significantly higher percentage of mismatches in the 0-6 h group, which clearly demonstrates the importance of HLA-matching, even if this results in a slightly longer ischaemia time. However, in the presence of good HLA-matches, the shorter the ischaemia time, the better is graft survival (6).

8.4.3 Abnormal lower urogenital tract

Recipients with abnormal bladders, who have received a kidney transplant following posterior urethral valve replacement, have an urinary infection rate of up to 60%, and a 5-year graft-survival rate of 5-15% less compared with normal bladders (1,5,8,11). The patient- and graft-survival rates following kidney transplantation in patients with urinary diversions (e.g., cystoplasties, conduits or pouches) are apparently similar to transplantations in normal bladders. However, it should be remembered that this conclusion is based on evidence from comparably smaller experiences (5,9,11,16) with transplantations in urinary diversions than with transplantations in normal bladders.

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9. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

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
ALG, ATG	anti-lymphocyte globulin
CAR	chronic allograft rejection
CDC	complement-dependent cytotoxicity test
CMV	cytomegalovirus
CT	computed tomography
CTS	Collaborative Transplant Study
CyA	cyclosporine A
DDT	dithiothreitol (test)
DRE	digital rectal examination
EBV	Epstein-Barr virus
EC	EuroCollins (solution)
EDTA	ethylenediaminetetra-acetic acid
EDHEP	European Donor Hospital Education Program
ELISA	enzyme-linked immunosorbent assay
ESWL	extracorporeal shockwave lithotripsy
GFR	glomerular filtration rate
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
HIV	human immunodeficiency virus
HLA	human leukocyte antigen, histocompatibility antigen
HTK	histidine-tryptophan-ketoglutarates
IL-2	interleukin-2
IVIG	intravenous immunoglobulin
LLDN	laparoscopic live donor nephrectomy
LURD	living unrelated donor
MMF	mycophenolate mofetil
MR	magnetic resonance
MRT	magnetic resonance tomography
NHBD	non-heartbeating donor
OKT3	anti-CD3 monoclonal antibody
PBS	phosphate-buffered sucrose
PRA	panel-reactive antibody
PSA	prostate-specific antigen
RCC	renal cell carcinoma
UW	University of Wisconsin (solution)