



European Association of Urology

GUIDELINES ON RENAL TRANSPLANTATION

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1 KIDNEY DONATION

1.1 EXPLANTATION TECHNIQUE

1.1.1 *Technique of cadaveric organ recovery*

RECOMMENDATIONS ON CADAVERIC ORGAN RECOVERY

1. In multiple organ recovery, good co-ordination and co-operation between various surgical teams are essential (Evidence level 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 (Evidence level B).
3. 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 (Evidence level B).
4. Retrieval of multiple intra-abdominal organs by 'en-bloc', total abdominal evisceration technique prevents warm ischaemia and traction injuries to the vascular tree (Evidence level B).

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). 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.

Preliminary dissection in the chest is often carried out by the cardiac team to isolate the aorta and superior vena cava before cannulation. The inferior vena cava is also isolated for easy access to allow quick venting of blood once in-situ perfusion has been initiated. For adequate perfusion of the liver, intestine, kidneys, and pancreas, the distal aorta is used for cannulation. Preliminary intra-abdominal dissection is performed to isolate the aorta, divide the bile duct, and ligate the gastroduodenal artery. If the lungs and/or heart are not to be recovered, aortic cross-clamping takes place in the abdomen. Some dissection of the supraceliac aorta may be necessary to allow clamping in this location. When the pancreas is not to be used as a solid organ for transplantation, the inferior mesenteric vein is dissected out and cannulated for portal perfusion of the liver, in addition to aortic perfusion. Two litres of the University of Wisconsin solution (UW) are used for each cannula. When the aorta alone is used for cannulation, 3 L of UW 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 is not extended 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 re-clamped 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 or misidentification of the vein as a portion of vena cava. 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, with mobilization of the small and large intestine to expose the kidneys, can jeopardize the liver by interfering with the venous return through the portal system. In addition, accidental injury or ligation of aberrant renal arteries can occur, 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 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, 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.

The retrieval of multiple intra-abdominal organs by an en-bloc total abdominal evisceration technique that prevents prolonged warm ischaemia and traction injuries to the vascular tree has been described in the literature (5). The technique was associated with a lower rate of primary non-function of livers, with no statistical difference in the incidence of delayed renal allograft function when compared with conventionally retrieved kidneys.

Improvements in techniques for harvesting organs from 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 (6, 7) have been followed by the development of different methods of aortic infusion techniques (8-10). Such methods of recovery have allowed good organs to be obtained from NHBDS in countries that do not have brain death laws (11).

1.1.2 *The living donor*

RECOMMENDATIONS ON LIVING 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 (Evidence level B).
2. Absolute criteria for donor's exclusion are to be respected and relative criteria for donor's exclusion should be adapted to specific situations (Evidence level C).
3. Donors with good post-operative outcome live longer and have a better quality of life than the general population of a similar age, despite the risk of hypertension or operative mortality risk (0.03%) (Evidence level B).
4. It is the surgeon's responsibility to ensure that the donor is medically, as well as psychologically suitable, for the procedure; the risks of donation are acceptably small; the donated organ is healthy; and the expectation of success in the recipient is reasonable.
5. Kidney harvesting through a transperitoneal approach has a higher number of splenic and intestinal complications (2.3%) compared with other surgical alternatives.
6. Subcostal extraperitoneal approach: access is quite difficult with this approach if the incision is small and the renal pedicle is deep in the wound. Dissection of the renal artery has to be carefully done as the incidence of vascular spasm is high (Evidence level C).
7. Dorsal lumbotomy is the preferred site of access in Europe. Nowadays, shorter incisions are used in order to minimize injury of the lumbar wall (Evidence level C).
8. The major elements that enable donors to accept the donation are the quality of surgery and an uneventful post-operative period. Less traumatic surgery for the donors (i.e. laparoscopic donor nephrectomy) increases significantly the number of new donors who wish to help their loved ones (Evidence level C).
9. It is advisable to obtain a psychiatric evaluation of the donor's motivation and his ability to understand the risks of the operation (Evidence level B).

At present, 20-25% of all kidney transplants performed in the world are with living donors. Most donors are closely related genetically. 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. Donation should be considered 'a gift of extraordinary value' (12).

Table 1: Advantages of living donation

-
- Better results (both long- and short-term)
 - Consistent early function and easier management
 - Avoidance of long waiting time for transplantation
 - Less aggressive immunosuppressive regimens
 - Emotional gain to donor
-

1.1.2.1 Evaluation

Evaluation for a potential donor 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.

Once all laboratory tests have been performed, the next step is renal arteriography with an excretion phase to visualize the collecting system. This eliminates the need for a separate intravenous pyelogram. 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 also is true for patients with advanced heart disease or a history of malignant neoplasia. Obesity may be a relative contraindication for any potential donor more than 30% above ideal body weight.

Table 2: Exclusion criteria for living donors

Absolute contraindications

-
- Age < 18 years
 - Hypertension (blood pressure > 140/90 mm Hg necessity for medication)
 - Diabetes (abnormal glucose tolerance test or HbA_{1C})
 - Proteinuria (> 300 mg/24 h)
 - Abnormal glomerular filtration rate (creatinine clearance < 75 mL/min)
 - Microscopic haematuria
 - History of thrombosis or thromboembolism
 - Medically significant illness (chronic lung disease, recent malignant tumour, heart disease)
 - History of bilateral kidney stones
-

Relative contraindications

-
- Abnormalities of the donor kidney (urological, vascular)
 - Obesity (30% or more above ideal weight)
 - Psychiatric disorders
-

HbA_{1C} = glycosylated haemoglobin.

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. Care must be taken to avoid leaving either the donor or the recipient with less than a perfect outcome.

1.1.2.2 Pre-operative management

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

After entering the operating room before the incision, the patient should receive a dose of an intravenous antibiotic; a third-generation cephalosporin, 1-2 g, is sufficient. Although pre-operative skin cleaning is recommended, hair clipping should be avoided until just before the incision.

1.1.2.3 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 (15-17):

- Classic transperitoneal approach, either through a midline, or through a left or right subcostal incision.
- Subcostal extraperitoneal approach (left or right).
- Dorsal lumbothomy 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 harvesting through transperitoneal approach: This technique is used more often in the USA and can be performed either through a midline or a subcostal incision (left or right). 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 (18-20) 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).

Kidney harvesting through subcostal extraperitoneal approach: A slightly curved incision is made from the tip of the 12th rib to the lateral borders of the rectus abdomini muscle at the level of the umbilicus. This type of incision avoids removal of a portion of the rib and results in less post-operative discomfort; it also avoids the possibility of pneumothorax.

Kidney harvesting through dorsal lumbothomy: Most European transplant centres recommend the harvesting of the left kidney from a living donor because of the longer length of the left renal vein. However, ultimately, the length of renal vein does not determine the choice of which kidney to harvest; other factors are more important in deciding which kidney to use, including the quality of the kidney, the presence of concomitant urinary or vascular abnormalities, and so on.

Depending on the position of the kidney in the retroperitoneum, which is assessed pre-operatively by radio-imaging studies, the line of incision will have a variable length and localization. If the kidney has a high position, an incision on the 12th rib, with its resection, is preferred. However, when the kidney is in a low position, a subcostal incision may be the choice. Before starting the incision, the anaesthesiologist has to increase the donor's diuresis, which is usually done by administering mannitol, 25 g. Currently, the anterior extension of the incision, which is done to allow a good exposure of the ureter, is unpopular in experienced centres. Shorter incisions are preferred in order to minimize injury to the lumbar wall. A good retraction and a proper intra-operative light will secure the surgical act, even through smaller lumbothomy incisions.

A kidney should never be retrieved with arterial spasm, or without diuresis.

After the renal vessels are clamped, rush and inappropriate gestures must be avoided. In a co-ordinated harvesting team warm ischaemia time is minimal. Do everything possible to ensure uneventful recovery of the patient by avoiding inappropriate intra-operative gestures.

Laparoscopic kidney harvesting: The major elements that enable donors to accept donation is the quality of surgery and the uneventful post-operative period after this major surgical act. Thus, less traumatic surgery for the donors 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 large amounts of fluids and mannitol to provide 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 dorsal lumbothomy position with the kidney bridge elevated either partially or totally, depending on whether a transperitoneal or retroperitoneal procedure is being used. The left kidney is preferred for laparoscopic harvesting by most experienced transplant centers because of the renal blood supply. The left kidney is chosen not only for the longer length of the left renal vein, but also for the fact that on the right side the liver may give rise to dissection problems.
- Transperitoneal laparoscopic approach - The transperitoneal approach offers more working space. The kidney is approached often by dissecting the left colon and peritoneum on different lengths. 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. In the opinion of most authors, if the gonadal vein is kept attached to the ureter, this will lower ureteral ischaemia after transplantation.
- 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 kidney has to be harvested in

good tonus and with highest urine output. The main drawback to this approach is the limited space for maneuver and the impossibility of being able to use endobags for quick kidney extraction.

1.1.2.4 Post-operative care

The post-operative care of a living donor is fairly standard. Adequate post-operative analgesia is the key factor in preventing post-operative complications, such as atelectasis and pneumonia (21-23). Infections should not occur with appropriate antibiotic prophylaxis. The continuous use of leg stockings and sequential compression devices are essential 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, as some patients 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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1.2 ORGAN PRESERVATION

RECOMMENDATIONS FOR ORGAN PRESERVATION

1. EuroCollins (EC) solution is in limited use today only for living donors and kidney-only cadaveric donors (Evidence level 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%) (Evidence level A)
3. Poor preservation may promote the onset of rejection (Evidence level B)
4. Better preservation of kidneys with immediate function after transplantation reduces significantly the cost of transplantation for each patient (Evidence level B).

1.2.1 *Period of organ preservation*

It is an ideal of transplantation that the period of effective organ preservation should be prolonged so that the transplant can be planned and carried out as a routine surgical procedure. In addition, a prolonged period of organ preservation may offer the opportunity for immunomodulation of the recipient prior to receiving the organ. An average adult kidney can be effectively stored for about 31 h, a liver for 12-18 h and a heart for only 4-6 h. 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.

1.2.2 *Methods of kidney preservation*

There are two methods of kidney preservation:

- Continuous hypothermic perfusion
- Initial flushing followed by ice storage.

1.2.2.1 *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 (Table 3) 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.

Ongoing trials with other preservation solutions, including histidine-tryptophan-ketoglutarate, Carolina rinse

solution, and a simplified UW-type solution, known as sodium lactobionate sucrose solution (10, 11).

Table 3: Composition of different flush solutions

Component (mmol)	Collin's	Sacks 2	Ross and Marshall	PBS	UW
Sodium	10	14	80	120	35
Potassium	115	126	80		125
Magnesium	30	8	35		5
Citrate			55		
Sulphate	30		35		5
Phosphate	50	60		60	25
Chloride	15	16			
Bicarbonate	10	20			100
Lactobionate					
Glucose	140				
Sucrose				140	
Raffinose					30
Mannitol		208	190		
Glutathione					3
Adenosine					5
Allopurinol					1
Hydroxyethyl starch					50 g/L
Dexamethasone					16 mg/L
Insulin					40 U/L
Penicillin					2x10 ⁵ U/L

PBS = phosphate buffered sucrose; UW = University of Wisconsin solution.

1.2.2.2 Choice of preservation method

Issues that must be considered by each transplant programme when selecting a method for kidney preservation, especially for cadaveric kidneys, include:

1. Any influence the choice might have on long-term outcome, apart from the direct effect on early graft function (12-14).
2. Suitability of the method for regional exchange of kidneys on the basis of established organ-sharing arrangements.
3. The cost of solutions, equipment and staff required for implementing the chosen method.
4. Average duration of preservation required (Table 4) (15-17).

Table 4: Ice storage after flushing versus machine perfusion (primary cadaveric transplants)

Function	All storage times		> 30 h storage		n		
	N		1 week	1 year		1 week	1 year
Machine perfusion	46		91.3%	81.4%	33	90.9%	80.1%
Ice storage	596		78.9%	83.9%	312	74.4%	76.6%

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1.3 POLICIES TO ENHANCE LIVING DONATION

RECOMMENDATIONS FOR POLICIES TO ENHANCE LIVING DONATIONS

1. The gap between donation and the demand for transplantation is widening. For many centers, especially in the USA, the only alternative is to use living donors. In some centers the number of kidneys obtained from living donors has exceeded the number of kidneys obtained from cadaver (Evidence level C).
2. Organ donation is voluntary and valuable and should be considered as 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 Honor, limited reimbursement, medical leave, priority access to organ for transplant, donor insurance) (Evidence level C).
3. The majority of transplant centers consider the contraindication for using grafts with anatomical abnormalities to be a relative contraindication. If a related donor has a good immunological correspondence with the recipient and the recipient has a poor toleration on haemodialysis, it is advisable to transplant the abnormal kidney leaving the donor with the best kidney (Evidence level C).
4. Laparoscopic nephrectomy offers donors less post-operative morbidity, quicker convalescence and better cosmetic results. It also increases the number of individuals willing to donate without increasing the risk to donors' safety or allograft function (Evidence level C).
5. Procurement of kidneys with multiple arteries can be accomplished safely without additional medical, social, economical, or post-operative clinical burden on the donor and the recipient (Evidence level B).
6. Plasmapheresis and intravenous immunoglobulin administration provide an effective rescue therapy for refractory humoral rejection and allow kidneys to be transplanted successfully into former cross-match-positive recipients (Evidence level B).
7. By using paired kidney exchange (with an equivalent exchange), the recipients benefit from a better match, reduced duration of dialysis, and expanded pool of living donors (within national laws). (Evidence level C)

The rate of living donation can be increased by two methods:

- Medical methods (see below) are represented by: laparoscopic harvesting, paired kidney exchange, transplantation of grafts with anatomical abnormalities (vascular, urinary tract, fusion), treatment with plasmapheresis and intravenous immunoglobulin administration.
- Ethical (by showing appreciation for organ donation) and organizational (such as medical leave for organ donation)

1.3.1 Ethical ways of showing appreciation for organ donation

Families of deceased donors often regard organ donation as a way of giving meaning to the donor's death or of allowing the person 'to live on' in others (1). As the organ donation is both voluntary and valuable, it should be considered as a charitable gift. Society could explicitly thank the organ donors for their gift, as is done with other charitable contributions, without jeopardizing its altruistic basis. New legislation should embrace ethically acceptable ways to encourage such charitable donations of organs.

1.3.1.1 Donor medal of honor

Organ procurement organizations have ceremonies which recognize and appreciate the organ donation. A donor medal of honor, 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 (2, 3).

1.3.1.2 Reimbursement for funeral expenses

There are authors who propose a governmental tax credit of \$10,000 for a cadaveric donation and a refund of, at least, \$2,500 for the donation of an organ from a living person (4, 5, 6). Both measures could be considered arbitrary, imposing monetary value upon an organ, and could be considered as a form of payment.

1.3.1.3 Organ exchange

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 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 (7), 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.

1.3.1.4 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 (8). In many countries, there is legislation that provides 30-day paid medical leave for all employees who donate an organ for transplantation (9). No one should have to incur a personal expense for donating an organ.

1.3.1.5 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 (10). The need for a transplant in a previous kidney donor should constitute the highest priority in the allocation of organs.

1.3.1.6 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.

1.3.2 Medical methods to increase number of living donations

1.3.2.1 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.

Table 5: Exclusion criteria for a potential living kidney donation

Kidney disease	
•	Reduced glomerular filtration rate, in comparison to normal range for age
•	Proteinuria of > 300 mg/day
•	Microhaematuria, except when an urological evaluation and a possible kidney biopsy are normal
•	Multiple kidney stones
•	Multiple cysts
•	Three or more arteries
•	Family history of autosomal dominant polycystic kidney disease (ADPKD), unless ultrasound or computed tomography (CT) scan is normal and donor age is > 30 years
•	Bilateral fibromuscular arterial dysplasia

1.3.2.2 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 much more direct and faster (Table 6) (11).

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 (Table 7). 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 the compared populations were similar, with respect to HLA-mismatches, number of related donors, presence of diabetes, previous transplant, gender and race.

Overall donor complications (Table 8) with the laparoscopic approach have compared favorably with previously reported series 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. A comparison of graft rejection and function between open and laparoscopic donation is shown in Table 9.

In conclusion, even though some researchers have argued that laparoscopic donation is unlikely to have an impact on donation, 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. Complications appear comparable to those reported in historic series using open surgery.

Table 6: 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

Table 7: Open versus laparoscopic donor nephrectomy

	Laparoscopic NX* n=110	Open NX N=48	p value
• Estimated blood loss (mL)	266±174	393±335	0.027
• Operative time (minutes)	232±33	183±27	<0.001
• Hospital stay (days)	3.0±0.9	5.7±1.7	<0.001
• Length of time analgesia used (days)			
• Oral narcotic agents**	4	12	<0.001
• Acetaminophen	3	17	<0.001
• Resumed oral feeding (days)	0.8±0.5	2.6±1.0	<0.001
• Returned to work (weeks)	4.0±2.3	6.4±3.1	0.003

* NX = nephrectomy.

** Amount of morphine equivalent (mg).

Table 8: Recipient morbidity

	Laparoscopic NX* n=110	Open NX N=48	p value
Hospital stay (median days)	7	7	NS**
Ureteral complications (%)	10 (9.1%)	3 (6.3%)	NS
Vascular thrombosis (%)	3 (2.7)	2 (4.2%)	NS
Rejection during the first month (%)	32 (29.0%)	15 (31.2%)	NS
Dialysis during the first week (%)	7 (6.4%)	3 (6.2%)	NS

* NX = nephrectomy.

** NS = not significant.

Table 9: Allograft rejection and function

	Laparoscopic NX* n=110	Open NX N=48	p value
No. of patients	110	48	
Rejection within 90 days	33 (30%)	17 (35.4%)	0.42
Onset of rejection (median no. of days post transplant)	8.0	8.5	0.48
Pathological findings			
Glomerulitis	0.6(1.0)	0.2(0.5)	0.24
Cellular infiltrate	2.1(0.8)	2.0(0.8)	0.77
Tubulitis	1.9(1.0)	1.8(1.0)	0.68
Intimal arteritis	0.5(0.7)	0.5(0.7)	0.63
Banff diagnostic category			
Score (1-4)	2.8(1.3)	2.7(1.8)	0.56
Creatinine clearance at 12 months (mL/min)	66	66	0.78

* NX = nephrectomy.

1.3.2.3 Acceptance of donor kidneys with multiple arteries and veins

The rapid increase in the number of laparoscopic kidney donations has produced a much higher rate of kidneys with multiple arteries. This fact has been accomplished by a significant shift in surgical practice (12-19).

Data collected from multiple centers of renal transplant have shown beyond doubt that the procurement of kidney with multiple arteries can be accomplished safely. The utilization of donors with multiple renal arteries

has increased the rate of donation by 30% in some centres.

1.3.2.4 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. Anti-HLA antibodies have been identified as the predominant cause of early graft failure from hyperacute rejection and acute humoral rejection.

Once the consequences of performing a transplant in the face of a circulating donor specific alloantibody were fully appreciated and routine pre-transplant cross-matching became standard, hyperacute rejection became exceptionally rare. However, there is a large population of highly sensitized patients who have little hope of receiving a transplant. Some of this population have potential living donors who meet standard criteria for transplantation but have a positive antihuman globulin cross-match (AHG) with their donors.

The combination of plasmapheresis and intravenous immunoglobulin under the cover of standard doses of cyclosporine, micophenolate mofetil and steroids can effectively and durably remove donor-specific anti-HLA antibody, thereby pre-emptively desensitizing recipients with positive cross-matches and allowing transplantation without hyperacute rejection (20).

The low rate and severity of antibody-mediated rejection in these patients previously sensitized to their donors' antigens may be the result of properties of the immunosuppression used. Micophenolate mofetil inhibits proliferation of B cells and blocks alloantibody production *in vitro*. Cyclosporin or Tacrolimus hydrate inhibit T-cell function, which could reduce helper T-cell function required for optimal production of mature B cells and plasma cells.

This pre-emptive therapy is initiated several weeks before a planned living-donor transplant. Our standard protocol was designed to include oral immunosuppression before the first plasmapheresis treatment, followed by a maximum of six plasmapheresis treatments on alternate days (Monday, Wednesday, Friday). The recipients also received 7 days of intravenous immunoglobulin (100 mg/kg/day).

1.3.2.5 Cross-over transplantation or paired kidney exchange

A cross-over renal transplantation or a paired kidney exchange transplantation is defined by a living kidney donation and an exchange between two or more couples who are hindered by ABO incompatibility or positive cross-match to donating their kidney directly to their recipients. However, the problem may be solved by cross-exchanging the kidneys between pairs of couples to make more matches.

The gap between the number of donors and the number of patients waiting for a kidney transplant continues to widen. Only a few patients receive transplants every year because of the organ shortage. Of course, these patients are also eligible to receive an organ from a living donor, such as a family member or a friend.

However, the pool of such kidneys has not been fully utilized, because not all the living donors are compatible with their recipients. Patients with available living donors continue dialysis and many die because of ABO incompatibility, positive cross-match, or low HLA-matching.

A step forward was made by Rapaport (21), who established the concept of kidney exchange between two donor receptor pairs in order to obtain the best compatibility. Thus, a spouse donor would give her kidney to an unrelated patient who matched her blood type. And that patient's spouse could then provide a kidney for the first donor's spouse. Such a swap may involve more than two donor receptor pairs in order to obtain the best compatibility.

The pairs of donor and recipient involved in a paired kidney exchange programme are interviewed to exclude any coercion of the donor. In addition, they are informed about the advantages and risks involved in a living donation and the donor's informed consent is obtained. In addition, all donors undergo psychological evaluation.

The inclusion criteria pursue the goal of exchanging equivalent kidneys with equivalent size, anatomy, similar renal function, and similar age. The donors are assessed pre-operatively by high-resolution intravenous pyelograms, quantitative renal nuclear scan, and spiral CT scan.

The basic principle of kidney exchange is the equivalent exchange. To accomplish this, a high-resolution pre-operative work-up is required so that unpredicted situations which can hinder harvesting are avoided. In this way, simultaneous harvesting is not mandatory.

If the algorithm of selection and evaluation respecting the principles of equivalence are accomplished, the method is feasible with good results.

By using paired kidney exchange, the recipient benefits from better matching, as well as 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 donation is the main source of organs, cross-over transplantation may become more popular as it increases 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.

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1.4 ETHICAL ISSUES IN TRANSPLANTATION

RECOMMENDATIONS ON ETHICS

1. It is the right of individuals to donate as well as to receive an organ (Evidence level B).
2. 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 (Evidence level C).
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 must be regarded as a 'regrettable necessity'. The justification for using living donors in renal transplantation is the continuing shortage of cadaveric donors (Evidence level 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 (1 death/4000 donations) (Evidence level B).
5. It is unwise to discuss brain death and the consequences with the patient's family without being able to answer their questions on organ donation (Evidence level B).
6. An individual 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 (Evidence level B).
7. 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 (Evidence level C).
8. Commercially motivated renal transplantation is unacceptable and the International Society of Transplantation strongly opposes their practice (Evidence level B).

1.4.1 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.

1.4.1.1 Beneficence: doing good

A central tenet of medical ethics is the obligation to strive at all the times to do good for the patient. Secondary obligations, which follow from acceptance of this principle, demand competence.

1.4.1.2 Non-maleficence: avoiding harm

Making sure that the balance between benefit and harm is appropriate is an important clinical judgment.

1.4.1.3 Respect for autonomy

Individuals should be treated as 'ends', not as 'means'. Respect for dignity, integrity and authenticity of the person is a basic human right. Patients with the capacity to understand relevant information (explained in simple language), to consider its implications and to come to a communicable decision are deemed to have decision-making capacity. Informed consent is central to the doctor-patient relationship.

1.4.1.4 Justice: promoting fairness

This principle is very important in the ethics of transplantation, where demand far outstrips supply. In that context, the allocation of organs requires a ranking system in order of priority, with philosophical justification for the method by which a patient's ranking is decided. In transplantation, scarce resources usually have to be allocated to recipients chosen from a larger pool of the population. How should this be done? There are two possibilities:

- Utilitarian approach: This always seeks to maximize the overall welfare of the group or to minimize the waste of resources. Many transplant services have allocation systems that select and organize allocation according to a limited number of criteria based on predicted outcome (HLA types). Other systems also operate very strict acceptance criteria.
- Discrimination on the basis of race, gender, age or 'social worth' obviously violates the principles of justice.

1.4.2 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, mainly predominantly brain-dead donors, but with NHBD procurement programme now used by a number of transplant centers.

This resource base is shrinking. This, in combination with the ever-increasing rise in potential recipients, is a cause of considerable pressure on transplantation programme.

1.4.2.1 *Cadaveric organ donor*

In most countries, obtaining consent to proceed with organ donation is a major barrier to be 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 undoubtedly influences organ donation favorably, but may be seen as intruding on individuals' rights.

The greater the experience of the persons asking for consent, whether they be an intensive care physician, neurosurgeon, transplant coordinator or social worker, the greater the chance that consent will be given. It should be remembered that **it is unwise to discuss brain death and the consequences with a patient's family without being 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.

Some developments and hospital authorities have attempted to bypass this reluctance by enforcing a 'required request' or 'routine inquiry'.

1.4.2.2 *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 the attributes of the recipient is not an accepted premise. Systems that involve attempts at welfare maximization are more generally acceptable. For example, one such model stratifies likely outcomes by criteria such as human leukocyte antigen (HLA) matching in kidney transplantation. This is a form of rule utilitarianism that meets some of the necessary criteria of justice, but of course not all.

From a deontological perspective, the patient's best interests are best served by supporting a transparent (respecting autonomy by communication and information sharing) system with a commitment to justice (which applies equally to your patient as well as others' patients).

The following ethical theories all have a part to play in implementing a transplantation policy:

- Utilitarianism: Utilitarian theories reference the rightness or wrongness of actions or policies to the good or bad consequences they generate. Current policies in kidney transplantation follow utilitarian theories extensively. A single principle, such as HLA-matching, is preferable to a complex work of rules and maxims.
- Egalitarianism: Egalitarian theories emphasize similarities or equalities amongst persons. Egalitarian approaches are not favored by professionals, but might be favored by the public, who do not see organ transplantation as only a therapeutic modality but also as a means of distributing a scarce common healthcare good. Surveillance of a standardized allocation policy of each transplant center within a region would also contribute to the acceptance of egalitarian ideas in the field of organ allocation.
- Libertarianism: Libertarian approaches to justice stand in stark contrast to the two previously discussed approaches. Whereas both utilitarianism and egalitarianism aim to sustain the common good, libertarian thinking denies the existence of a common good altogether. Libertarian values and cardinal virtues are all valued but only liberty is considered to be a fundamental human right (7). There is room for a libertarian approach in organ allocation in situations of acute developing clinical urgency (e.g. heart and liver transplantation), when the responsible transplant surgeon has to make a definitive, final, bedside decision for his patient without considering other patients on the waiting list.

1.4.3 *Living donors*

The ethical approach to organ donation is conditioned principally by those rules that seek to confer benefit 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 been regarded as a regrettable necessity. In fact, there is a widely held view among members of the transplant profession that the only justification for the use of living donors in renal transplantation is the continuing shortage of cadaveric donors (8).

1.4.3.1 *Coercion of related altruistic donors*

A foundation stone 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 all developed countries to prevent payments for living related organs.

There are several issues to consider:

1. There are two terms, which are frequently used in debate of this subject (7): 'obligation' and 'duty':
 - An obligation is an externally applied restriction of an individual's right to choose to donate. This category is used within families as well as between unrelated people.
 - Duty, however, is defined as an internal motivation arising from love, friendship or respect for another individual.
2. When considering a potential, living-related kidney donation, the transplant surgeon has to handle the situation with great care. Any attempt at coercion, such as a forceful presentation of the medical advantages of transplantation, should be avoided.
3. The altruistic living donor must, of course, give informed consent, which can be only obtained if he has a proper understanding of the risks involved.
4. Donation of organs from related, mentally incompetent adults or children is forbidden by law in most developed countries.
5. Altruistic donation by a family member or an emotionally related person (wife or friend) typically has a psychological benefit for the donor, with only a few (8%) later regretting their act of donation.

1.4.3.2 *Payment of living non-related donors for their 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.

The recommendations with regard to the WHO statement are as follows:

1. A full understanding of the risk is essential for properly informed consent to any form of surgery. Since paid organ donors will always be relatively poor and may be underprivileged and undereducated, the donor's full understanding of these risks cannot be guaranteed. Laws are therefore required to protect these individuals from exploitation.
2. We believe that operations should be performed because of therapeutic indication, and not for the acquisition of money.
3. A rewarded donor from an impoverished background cannot be presumed to give proper voluntary consent since the coercive influence of a substantial payment is likely to distort the balance of risk versus the benefit in a person's mind.
4. In a free market for organs, profit is the first objective and medical standards will fall, no matter how well regulated the market is.
5. Legally paid donation would undermine altruistic donation.
6. Traffic in organs divides society in that the donor will always be relatively poor and the recipient relatively rich.
7. Treating the body as a commodity is objectionable.

Perhaps the most difficult aspect of this debate is the knowledge that, although the ethical principles may be easily agreed, their consistent application, through both legislation and social and cultural acceptance, is a difficult goal.

1.4.4 *Conclusion*

Transplantation is full of ethical dilemmas. Just as surgeons catch up with the new developments of yesterday, they face further new scenarios for which there is no precedent. In this context, therefore, the structured application of the general principles of medical ethics and bioethics is more than a casual, intellectual exercise. It is a necessary tool that helps to describe our dilemmas, analyze the important elements, and formulate strategies to deal with the real-life issues found in everyday practice.

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1.5 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 cause a plateau in the kidney transplant waiting lists, and in the case of Spain, a decrease (1). Elsewhere in Europe, cadaveric kidney donation rates have been static or have declined since 1989. Table 10 lists the kidney transplant rates in 2001 for various European countries (6).

Table 10 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, which data from successful countries had suggested could be 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 organisations should aim. Nevertheless, it is possible to include some options for action, which are described below.

1.5.1 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 more efficient use of scarce 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 3,000 (7).
- If legally permitted, living unrelated donors should be encouraged.

RECOMMENDATIONS 1.5a

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 intergrate and oversee the exhaustive process of donor selection and health checks within a family.

1.5.1.1 *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 1.5b

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

1.5.1.2 *'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 contraversional, 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.

1.5.1.3 *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 1.5c

Legislation in every European country currently forbids this.

1.5.2 *Approach 2: Increase supply and use of cadaveric kidneys*

1.5.2.1 *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 is 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 coordinators should be mandated to access the register routinely to identify the wishes of potential cadaveric donors.

RECOMMENDATION 1.5d

In all countries without presumed consent law, further efforts should be made to recruit donors through an opting-in register or by carrying cards.

1.5.2.2 *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 (European Donor Hospital Education Programme) or sufficiated 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 1.5e

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 an institutional audits such as Donor Action.

1.5.2.3 'Opting-out' legislation

The introduction of 'opting out' legislation appears on first sight of 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. In France, however, opting-out legislation has not achieved such successful donation rates. This may be because France chose initially 'hard-line' opting out, in which donation takes place if a donor has not opted out, irrespective of the family's wishes. Adverse publicity led to a softening of the practice, with a consequent increase 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 1.5f

In our view it is not possible for these guidelines to make a recommendation about something as fundamental as changing the law on cadaver donation.

1.5.2.4 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) presumed consent legislation 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 1.5g

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.

1.5.2.5 Elderly donors

Older donors: Although the long-term survival of kidneys from elderly donors (over 60 years old) 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 1.5 h

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

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1.6 Kidney donor selection and refusal criteria

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

1. Any brain death comatose subject should be considered a potential organ donor, without age limits (Evidence level 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 (Evidence level 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 (Evidence level 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 old subjects to expand the pool of donors, the donors must be evaluated according to age, vascular conditions and renal function. 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, as organs 'that nobody wants', they 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 (Evidence level B).

1.6.1 Recommendation 1

Any brain death comatose subject should be considered a potential organ donor, without age limits (Evidence level C).

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 results seem to be inferior (1). In addition, the main surgery-related 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 an usable organ. Thus, there are now no absolute age limits to donation. However, since older donors present more co-morbidity, 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).

1.6.2 Recommendation 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 (Evidence level C).

Before beginning the operation to retrieve the organs, authorization by the donor's relatives or significant others 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.

1.6.3 Recommendation 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 (Evidence level B).

The following donor infections or malignant tumours represent absolute contraindications to donation.

1.6.3.1 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, infection 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.

1.6.3.2 Special exceptions for infections

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

HBsAg-positive donor: In a HBsAg-positive recipient (if HDV antigen is negative), transplant is allowed after informed consent. In a HBsAg-negative recipient with anti-HBsAg antibody titre ≥ 10 mIU/ml, transplant is allowed after informed consent. In a 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.

HBcAg-positive donor (donor with hepatitis B IgG core antibody): In liver transplantation, the risk of transmitting hepatitis B from a 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.

1.6.3.3 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.

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, occasional kidney cancers, which were completely excised. Such patients require very careful follow-up (6).

1.6.3.4 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.

Potential recipients affected by the following low-grade (grades 1 and 2) brain tumours are suitable for transplantation (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.

1.6.4 Recommendation 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 old subjects to expand the pool of donors, the donors must be evaluated according to age, vascular conditions and renal function. 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, as organs 'that nobody wants', they 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 (Evidence level B).

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 11).

Table 11: 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	
Arterial sclerosis	

1.6.5 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 whereas short-term results are 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 of 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.
- 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).

1.6.6 *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, the question arises as to which organs might be used for a double graft in a single recipient. The answer must be pairs of kidneys that otherwise would be discarded based on functional or histological aspects (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 (29) concludes that double-kidney transplants are safe, well tolerated and result in no more surgical complications than single-graft operations. Nevertheless, the conclusions of evidence-based medicine concerning dual-kidney transplantation indicate 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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2. KIDNEY RECIPIENT

2.1 PRE-TRANSPLANT THERAPY

2.1.1 Abnormal urogenital tract

RECOMMENDATIONS (EVIDENCE LEVEL 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 (vertebral/vascular anomalies, anal atresia, tracheo-esophageal fistula, esophageal 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, supravescical 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).

2.1.2 Urinary diversion

In patients with absent bladder (e. g. cystectomy for bladder cancer) or sphincter insufficiency (e. g. neurogenic, iatrogenic), supravescical 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 supravescical 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).

2.1.3 Indications for pre-transplant nephrectomy

2.1.3.1 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).

2.1.3.2 Medically refractory hypertension

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

2.1.3.3 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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2.2 Selection and refusal criteria

2.2.1 Co-morbidity

Co-morbid conditions, such as diabetes mellitus or cardiovascular disease, are known to have a major impact on the morbidity and mortality of kidney transplant patients (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.

2.2.2 Cardiovascular disease

2.2.2.1 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).

2.2.2.2 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).

2.2.2.3 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.

2.2.3 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.

2.2.4 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 12 lists the recurrence rates of the most important diseases.

Table 12: Recurrence rates and graft survival with recurrent disease

Disease	Recurrence rate	Graft survival with recurrent disease	Treatment options
IgA-glomerulonephritis	50% after 5 years ~ 100 % after 20 years	15% lower graft survival 5 years post transplant	ACE inhibitors (cyclophosphamide, 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 immuno-suppression 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

2.2.5 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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2.3 Transplantation in pregnancy

RECOMMENDATIONS ON KIDNEY TRANSPLANTATION IN PREGNANCY

1. 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 (Evidence level B).
2. 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 (Evidence level B).
3. 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 (Evidence level C).
4. Controls should focus on hypertension (pre-eclampsia affects 30% of patients), proteinuria, renal function, rejection and infection (Evidence level B).
5. Although vaginal delivery is possible, the rate of Caesarian section is high (50%). Breast feeding is not suggested because of the potential risk to the child of ingesting immunosuppressive agents (Evidence level C).

2.3.1 RECOMMENDATION 1

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 (Evidence level B).

2.3.1.1 Discussion

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 (2-5,6).

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 of pre-term delivery (increased by 50%) and their offspring have a lower birthweight (increased by 20%) (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.

2.3.2 Recommendation 2

Pregnancy should be planned at a moment of good general and graft health, when renal function and immunosuppressive therapy are stabilized and there are no signs of rejection, hypertension, proteinuria, hydronephrosis or chronic infection (Evidence level B).

2.3.2.1 Discussion

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 increases the risk during pregnancy, because it 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.

2.3.3 Recommendation 3

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 (Evidence level C).

2.3.3.1 Discussion

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 pharmacokinetics. 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 mycophenolate mofetil, which is contraindicated, as is, sirolimus.

2.3.4 Recommendation 4

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

2.3.4.1 Discussion

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 birthweight 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 progression 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).

2.3.5 Recommendation 5

Although vaginal delivery is possible, the rate of Caesarian section is high (50%). Breast feeding is not suggested because of the potential risk to the child of ingesting immunosuppressive agents (Evidence level C).

2.3.5.1 Discussion

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 birthweight. 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.

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3 TRANSPLANTATION TECHNIQUES

3.1 KIDNEY TRANSPLANTATION

3.1.1 Transplant preparation

On the back table on a sterile iced bed at +4°C.

3.1.1.1 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.

3.1.1.2 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.

3.1.1.3 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 to reduce the duration of the vascular anastomosis (4, 8, 35).

3.1.1.4 Ureter

- Check for double ureter.
- Keep the peri-pyelic and peri-ureteral fat in place, which includes the ureteral vessels.

3.1.2 Technique in adults

3.1.2.1 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.

3.1.2.2 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 the vessels to be transplanted are in a good position in the recipient.
- Both anastomoses are performed with two halves of running non-absorbable monofilament 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).

3.1.2.3 Ureter anastomosis

- Ureterovesical extravascular 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.

3.1.3 Special cases

3.1.3.1 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.

3.1.3.2 *Depending on the vascular state of the recipient*

If the iliac arteries do not allow clamping:

- Do an endarterectomy of all of the iliac axis and fix the intima by U-shape sutures before performing the anastomosis.
- If an endarterectomy 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.

3.1.3.3 *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).

3.1.4. *Early complications*

3.1.4.1 *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.

3.1.4.2 *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. Caliceal fistulae are treated by nephrostomy or vesical catheter and double-J-stent. If this fails, polar nephrectomy can be tried (23).

RECOMMENDATIONS

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

3.1.4.3 *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 h with success.

RECOMMENDATIONS

- Preserve the aortic patch.
- Look for intimal rupture before anastomosing the kidney.
- Avoid plicature of the artery.
- 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, eventually with sutured stitches.

3.1.4.4 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

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

3.1.5. Late complications

3.1.5.1 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 bad 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

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

3.1.5.2 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

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

3.1.5.3 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.
- Caliceal and smaller renal stones should be removed by extracorporeal shockwave lithotripsy (ESWL).
- Larger caliceal 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

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

3.1.5.4 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

- Remove an arterial patch from the donor and use it for the transplant. (17).
- Examine the artery intima, fix the intima, or re-cut the artery, in case of lesions.
- 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.
- Avoid anastomoses which are too tight, and cut out a small piece of the arterial wall for re-implantation.

3.1.5.5 Arterio-venous fistulae or arterio-caliceal 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.

3.1.5.6 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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3.2 KIDNEY AND PANCREAS TRANSPLANTATION

3.2.1 Introduction

Simultaneous pancreas-kidney transplantation (SPK) is the treatment of choice for patients with type I diabetes mellitus associated with chronic renal failure. It is considered to be the best therapeutic option to achieve blood

glucose control and insulin independence in uraemic or post-uraemic type I diabetes patients because it protects the transplanted kidney from recurrent diabetic glomerulopathy. As a result of improvements in surgical techniques, immunosuppression and patient selection, 1-year survival rates of 95%, 83%, and 88% for patient, pancreas, and kidney survival, respectively, are reported for patients who have undergone SPK.

These results with a complete pancreatic and kidney transplant are superior to those of a kidney transplant alone. Kidney survival rates for 8 years in diabetic patients are 86% for SPK and 47% for kidney transplant alone (KTA) (7, 11). Furthermore, glycaemic control is significantly better in the SPK group, than in the KTA group.

3.2.2 Donor selection

Pancreas donors must be young, less than 45 years old, not obese and with well-functioning kidneys. Exclusion criteria are alcoholism, diabetes, and acute or chronic renal failure.

The whole pancreas is removed, with the second duodenum, the coeliac trunk and the superior mesenteric artery on an aortic patch. When the coeliac trunk cannot be used, a bifurcation of the iliac artery is taken in order to perform a 'Y' arterial repair. The mesenteric and splenic arteries are sutured on the two legs of the arterial graft. An external iliac vein must be removed to lengthen the portal vein.

3.2.3 Recipient

The recipient is a patient with type I diabetes mellitus associated with chronic renal failure (6). Contraindications include chronic illness, polyarteriopathy, and non-dilatable coronaropathy.

3.2.4 Technical aspects

The abdominal cavity is open using a xipho-pubic median incision, through which the pancreas is transplanted into the peritoneal cavity. The kidney can be placed in an intra- or extraperitoneal location using the same incision. The extraperitoneal position allows a very safe and comfortable access for renal biopsy.

3.2.4.1 Vascular technique

The pancreatic vessels are anastomosed into the very initial part of the vena cava and the common right iliac artery or into the right external iliac vessels using non-absorbable polypropylene running sutures.

3.2.4.2 Re-implantation of the portal vein

The portal vein must be lengthened with a segment of the external or common iliac vein. This can be done in two ways:

- In the inferior vena cava (systemic re-implantation): the insulin goes through the vena cava directly to the heart.
- In the portal system into the superior mesenteric vein (portal re-implantation): the insulin goes directly into the liver (2).

Most techniques use systemic re-implantation because no significant difference has been reported according to the type of venous drainage but this remains a debated topic (10, 16, 17).

3.2.4.3 Drainage of pancreatic secretions

Drainage of pancreatic secretions is accomplished as follows:

- The second duodenum is procured with the pancreas.
- The two ends of the second duodenum are closed with an automatic stapler and a double layer of non-absorbable polypropylene running suture.

3.2.4.4 Transplant in the intestine (enteric drainage)

The duodenum is anastomosed side-to-side into the jejunum using a double-layer running suture (external non-absorbable and internal absorbable).

3.2.4.5 Transplant in the bladder (bladder drainage)

The duodenum is anastomosed sideways into the bladder in two layers.

The bladder collects pancreatic and duodenal secretions, composed of water, sodium bicarbonate and pancreatic enzymes (9, 13).

There is no difference in graft-survival rates for the pancreatic transplant between duodenal drainage into the intestine and drainage into the bladder. However, bladder drainage has now been abandoned due to very high rate of urological complications (5).

3.2.4.6 Transplant of pancreatic islets

The transplant of pancreatic cells is a non-invasive alternative technique capable of restoring cellular function.

It has a higher 1-year graft-survival rate than transplantation of the pancreatic gland.

The technique poses some difficult technical problems:

- Isolation of the islets and collection after digestion of the pancreas
- Separation of the islets from the exocrine tissue by centrifugation
- Injection of the islets into the portal system by catheterisation of the portal vein.

In addition, the fresh islets must be transplanted immediately. The quantity of islets to be transfused is 12000 islets/kg.

3.2.5 Complications

3.2.5.1 Venous or arterial thrombosis

The risk of venous or arterial thrombosis is 15%.

Treatment:

- Heparin.
- Thrombo-aspiration (3).
- Transplantectomy.

RECOMMENDATIONS

- Avoid all excessive manipulation of the pancreatic gland during procurement (4).
- Initially, take an aortic patch to support the coeliac trunk and the superior mesenteric artery to make an easier repair.
- Make a large venous anastomosis.
- Avoid post-operative dehydration and hypotension.
- Avoid getting the patient up before 3 days post-operatively to avoid a low pancreatic vascular flow which may promote vascular thrombosis.
- Anticoagulation.

3.2.5.2 Arterio-venous fistulae (pseudo-aneurysm) of the mesenteric artery

These are very rare; diagnosis is made by arteriography.

Treatment:

- Embolization or surgical repair (8, 18).

RECOMMENDATION

- Perform separate ligations of the superior mesenteric artery and vein during procurement.

3.2.5.3 Pancreatitis

Pancreatitis may be caused by:

- Ischaemic reperfusion lesions (4).
- Reflux into the pancreatic ducts.

Treatment:

- Sandostatin (12, 15).

RECOMMENDATIONS

- Minimize manipulation of the pancreas during procurement.
- Transplant with a short, cold ischaemic time of less than 12 h.

3.2.5.4 Duodenal or vesical fistulae

- Following a surgical problem.
- A pancreatic fistulae is diagnosed by the drainage of urine and amylase.

Treatment:

- Surgical closure of the fistula.
- Bladder aspiration if bladder drainage.

RECOMMENDATIONS

- Close the two duodenal ends using automatic staplers and make the vesico-duodenal anastomosis with two layers of 4x0 Prolene.

3.2.5.5 Digestive complications

Re-implantation in the intestine may lead to specific digestive complications:

- Digestive fistulae.
- Peritonitis.
- Parietal suppuration.
- Occlusion through adhesion.

Treatment:

- Early surgical repair.
- Fistula: surgical closure.
- Occlusion: removing the adhesion.

RECOMMENDATIONS

- Lateral digestive anastomosis in two planes allows good placement of digestive sutures.
- Put the pancreas under the ileum.

3.2.5.6 Urinary complications

Urinary complications are specific to the transplant drained into the bladder. Drainage into the bladder can give rise to urinary infections, haematuria, reflux pancreatitis and acidosis. These complications are secondary to bladder-emptying problems due to diabetic bladder neuropathy, and include:

- Urinary infections, which occur in 60% of cases, and include urethritis, cystitis (common), or asymptomatic bacteriuria.
- Haematuria, which is quite common and is normally treated with vesical irrigation.
- Balanitis, urethritis or cystitis: exceptional and caused by enzyme activity.
- Metabolic problems, which include metabolic acidosis due to voiding of bicarbonates, loss of water, salt and bicarbonate, for which the regulatory mechanisms of the renal system cannot always compensate.

Treatment:

- Self-catheterization.
- Treatment of metabolic problems is with sodium bicarbonate tablets.
- If treatment fails, the duodenum should be diverted into the intestine (1, 14) to avoid amylase coming into contact with the bladder and the urethra.

RECOMMENDATIONS

- Urodynamic evaluation before combined kidney and pancreas transplantation.
- If the evaluation confirms a diabetic bladder neuropathy, endoscopic cervicotomy with, eventually, reduction cystoplasty may reduce complications.
- Bladder drainage must occur only into a perfectly functioning bladder when enteric drainage is not possible.

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3.3 Kidney transplantation in abnormal urogenital tract

RECOMMENDATIONS (EVIDENCE LEVEL B/C)

- 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).
- In ureterocystoplasty, it is feasible to perform uretero-ureterostomy with one of the patient's own ureters (1).
- In patients with continent ileocolic 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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4 MATCHING OF DONORS AND RECIPIENTS

4.1 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.

4.1.1 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).

4.2 Cross matching

To avoid hyper-acute rejection of kidney transplant T-cells, a cross match test must be performed before each kidney transplantation. 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).

4.3 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.

4.4 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.

4.5 Viral disease

4.5.1 Cytomegalovirus (CMV)

Cytomegalovirus infection is the most common viral disease after 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 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 detected usually after 4-5 weeks post transplant. Thus, in these recipients, adequate prophylaxis with gancyclovir 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.

4.5.2 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 immunosuppression 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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5. IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION

5.1 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 unselective 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, 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 longterm use may be a cause of recent in chronic allograft nephropathy. It also causes hypercholesterolaemia, hypertension, gum hypertrophy, hirsutism 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 mycophenolic 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. However, 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 longterm 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 randomised controlled trials (RCTs) to reduce the prevalence of acute cellular rejection by approximately 50% (13, 14).

5.2 Primary Immunosuppressive Prophylaxis

5.2.1 Cyclosporine A

Modern therapy is based on cyclosporine A, used together with more recent drugs, such as MMF 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 the Table 13 (1, 2).

Table 13: Randomised controlled studies of Cyclosporin A

REF	REGIMEN	CONTROL EXP	n	EXP	ACR CONTROL	GRAFT SURVIVAL EXP	CONTROL	PATIENT SURVIVAL EXP	CONTROL	COMPLICATIONS
1	CyA 20 mg/kg/day and Imuran & Steroid	Imuran & Steroid	103/110			*69% (3 years)	58%	90%	86%	Higher creatinine in Exp. group
2	CyA 20 mg monotherapy	Imuran & Steroid	117/115			*67% (3 years)	49%	90%	83%	Higher creatinine in Exp. group
5	Tacrolimus + Imuran + Steroid	CyA & Im & Pred	205/207	*31%	46%	91% (3years)	88%	96%	97%	Tacrolimus assoc with 20% diabetes
6	Tac & Im & Pred	CyA & Im & Pred	303/145	*26%	46%	82% (3years)	86%	93%	96%	
7	Cya Neoral & Im & Pred	Tac & Im & Pred	40/40	33%	40%	-	-	-	-	
* P < 0.05										

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 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).

5.2.2 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 underdosing, which may lead to rejection. Tacrolimus and cyclosporine have been compared in prospective, randomized studies (see table 13) (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 was 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 randomised 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 $>150 \mu\text{mol/l}$ 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 13. 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.

5.2.3 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 3 g/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 significant 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 (RCT) of 187 renal transplant patients receiving triple therapy (cyclosporine, MMF 2G per day and steroids) compared creatinine clearance, rejection rate and serum cholesterol 6 months after stopping cyclosporine in the experimental group. 8 mild and 1 severe rejections occurred after CsA withdrawal all of which were reversed, compared to 2 episodes in the controlled group ($p=0.03$). Excluding those cases of rejection, mean creatinine clearance was higher in those who stopped CsA ($+7.5\text{ml/min}$, $p=0.02$). In the intention- to- treat population, CsA withdrawal was associated with a lower total serum cholesterol and LDL ($p=0.015$). It is to be hoped that macrolide-reducing regimens will result in a reduction of chronic allograft nephropathy.

SIROLIMUS was licenced for clinical use in 1999 by the FDA and as an adjunct to cyclosporine therapy in Europe in 2002. The drug, a non-nephrotoxic, broadly reactive anti-proliferative for rejection, has been found to act synergistically with, and be equipotent to, cyclosporine. It shows dose- dependent, reversible thrombocytopenia and hypercholesterolaemia (17). The first large multi-centre RCT compared Sirolimus (Rapamune) with Azathioprine in CsA- treated renal transplant recipients (18): although rejection frequency and severity were reduced, renal function was better at one year in the Azathioprine- treated group, an effect which appeared independent of blood cyclosporine levels. A smaller RCT 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 one year in the Sirolimus- treated patients (19). A similar trial (20) compared Sirolimus with CsA 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 RCT (17) studied efficacy and safety of cyclosporine withdrawal at 3 months from a cyclosporine plus Sirolimus maintenance regimen, compared with non-withdrawal: though acute rejection was significantly more frequent after CsA withdrawal ($9.8\% \text{ v } 4.2\%$ $p=0.035$) renal function and blood pressure was improved in this group and more viral infections were seen in the control patients. As small single-centre RCT (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 CsA and Sirolimus based regimens up to 1 year post transplant. Longterm follow up has not yet been reported with Sirolimus. Though its record as a potent agent against early rejection seems impressive, it is not yet known whether a reduction in CAN will be a longterm result of its use.

5.3 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 it 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 practitioner's 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.

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6 COMPLICATIONS

6.1 Immunological complications

6.1.1 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 14), and form the basis for deciding prognosis and treatment.

Table 14: 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.

6.1.2 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.

6.1.2.1 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.

6.1.2.2 Treatment

Hyper-acute rejection is treated by graft nephrectomy.

6.1.2.3 Prevention

Hyper-acute rejection can be prevented by the avoidance of 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 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 transporting of kidneys to recipients with a cross match that is very likely to be positive.

6.2 RECOMMENDATIONS

- ABO incompatibility should always be avoided between the donor and recipient.
- 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.

6.2.1 Acute allograft rejection

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

6.2.1.1 T-cell mediated acute rejection (Table 15)

Table 15: T-cell mediated (acute cellular rejection, ACR)

T-cell mediated rejection (acute cellular rejection, ACR)	
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)

6.2.1.2 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 pyrexia, 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, Biopsy gun).

6.2.1.3 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.

6.2.2 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.

6.2.2.1 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.

RECOMMENDATIONS

- Renal transplant practitioners must be continuously aware of the possibility of acute rejection, particularly during the first 6 months after renal transplantation.
- During hospitalization, daily blood and urine samples should be taken for renal and haematological studies and the patient should be examined.
- There should be a high index of suspicion for rejection in any patient who suffers fever, graft tenderness, or reduced urine output.
- There should be routine access to ultrasound-guided biopsy of the transplant, and there should be

sufficient expertise in the hospital pathology department to allow a clear-cut diagnosis of rejection, or other type of allograft dysfunction.

- 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.
- In patients who suffer ACR, they should be tested as soon as possible for the presence of anti-HLA IgG antibodies reactive with the graft, by CDC cross matching.

6.2.3 *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 (DDT) 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 (2 h) 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 (FAT) 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).

RECOMMENDATIONS

- All centres practising renal transplantation should have access to elective serological profiling of all potential, and actual, waiting-list recipients to define the percentage and specificity of panel reactive antibodies (PRA), and their isotypes, IgG or IgM.
- 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).

6.2.4 *Chronic allograft rejection (humoral or unknown pathogenesis)*

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).

6.2.3.1 *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.

RECOMMENDATIONS

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

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6.4 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.

6.4.1 *Prior malignancy in the recipient*

This situation can be due to:

- Relapse of a prior neoplasia.
- A latent asymptomatic neoplasia.

6.4.1.1 *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.

More than 2 years:

- Large and high-grade RCC.
- Invasive or in situ 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 16.

Table 16: 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, in invasive cancers with 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.

6.4.1.2 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 and a biopsy are indicated for high risk patients.
- Chest X-ray.
- Abdominal ultrasound, to exclude neoplasia.

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.

6.4.2 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, malignancy (6,11,12,13).

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 the case of transplanting a kidney with a non-visualized tumour, graft nephrectomy and suspension of immunosuppression are mandatory. In order to prevent this occurring it is recommended to carry out a renal ultrasound in the donor.

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. Whether screening for prostate cancer is carried out differs from country to country, it is recommended only if there are pre-existing grounds to carry out such a test.

6.4.3 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, especially in Southern regions (16).
- Analgesic abuse: urothelial cancer.
- Dialysis-acquired cystic renal disease: renal cancer.
- Immunosuppressors, such as cyclosporine A (CsA) 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.

6.4.3.1 Annual screening measures

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

6.4.3.2 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 daily total sun block are recommended for kidney transplant recipients, especially those living in sunny regions.

6.4.3.3 Nodal examination

The incidence of lymphoproliferative diseases (1-2.5%) has increased since the introduction of cyclosporine (CsA), 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.

6.4.3.4 Gynaecological evaluation

Cervical cancer is 3-16 fold higher than in the general population and in 70% corresponds to in-situ carcinoma. 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.

6.4.3.5 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 prostate-specific antigen (PSA) screening is performed in males with a renal transplant. All recipients over 50 year of ages are required to have an annual PSA and digital rectal examination (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).

6.4.3.6 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: carcinoembryonic antigens (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).

6.4.3.7 Urinary cytology

It is mandatory in patients with a previous history of transitional cell carcinoma or hematuria. The incidence of urothelial tumours is three-fold higher than in the general population. The tumours are usually transitional cell neoplasia, although the incidence of bladder adenocarcinoma and nephrogenic adenoma has also increased. Urinary cytology is mandatory in patients with macro- or microhaematuria, analgesic nephropathy, or a prior history of urothelial cancer (2). In cases of positive cytology or microhematuria a cystoscopy is to be carried out.

6.4.3.8 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.

6.4.4 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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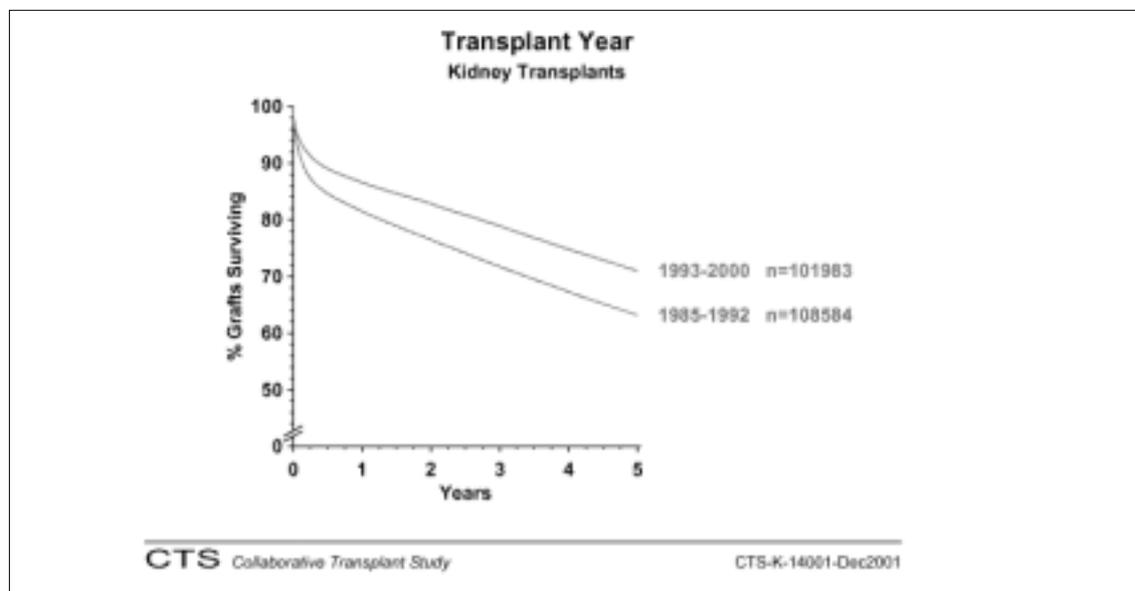
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7 GRAFT AND PATIENT SURVIVAL

RECOMMENDATIONS FOR GRAFT AND PATIENT SURVIVAL (EVIDENCE LEVEL B)

- 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, 13, 17) (Figure 1).
- 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, 13, 17).

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:

7.1 Cadaver and living donors

7.1.1 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 cadaver kidneys. The 3-year graft survival of living-donor kidney transplantation is 90% for HLA-identical siblings, 80-85% for 1-haplotype-identical related, 85% for spouses, and at least 80% for living, unrelated, unmarried donors, compared with 70% for cadaver kidneys.

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 (CTS, 13, 14). Husband-to-wife and wife-to-husband transplantations show similar results with 3-year graft survival of 87% if the wife as recipient has not been pregnant before. In case of a former pregnancy, the outcome is approximately 10% worse (16).

Five-year graft survival is approximately 84% for siblings, 77% for unselected kidney living donors, and 63-66% for cadaver kidneys (CTS, 4). Ten-year graft survival following HLA-identical living donors is 78% for patients with polycystic kidney degeneration and 60% for patients with diabetes (17).

7.1.2 Patient survival

In addition, patient survival following living-donor kidney transplantation is at least 95% after 1 year and 90% after 5 years. This is better than patient survival following cadaver kidney transplantation with a 1-year survival rate of 90% and a 5-year survival rate of about 80% (CTS, 2, 4, 10, 13, 14).

7.2 Age of Donor and Recipient

7.2.1 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 (CTS, 3,4).

Delayed function is also about 20% higher following kidney transplantation of donors older than 65 years compared to donors less than 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 (4,16,17).

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 (CTS, 12,13,17).

7.2.2 Recipient's age

In addition, the recipient's age has an important impact on the outcome of transplantation. 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 (CTS). 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 rates. It is not clear yet how important it is to have HLA-matching in this 'old for old' group (18).

7.3 HLA-matching

Both the Collaborative Transplant Study (CTS) 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).

Even with 'modern' immunosuppressive agents, including the drugs tacrolimus (FK 506), mycophenolate mofetil (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 (CTS,13,14).

7.4 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 (13). As mentioned above, the use of 'modern' immunosuppressive drugs in different combinations has not yet improved the outcome significantly.

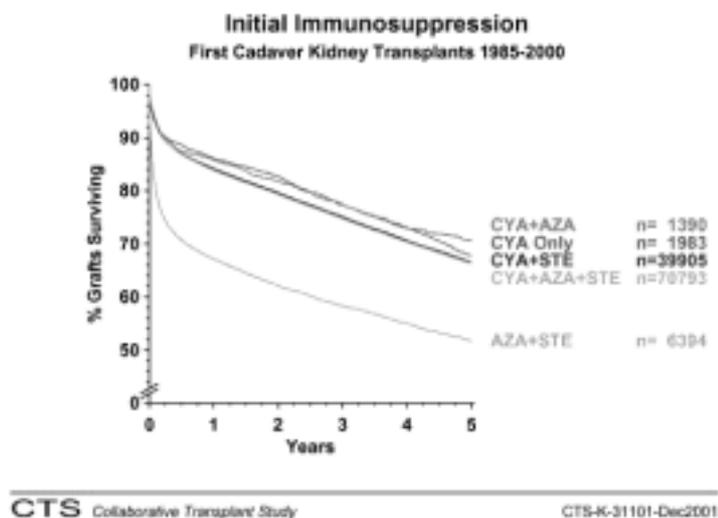


Figure 2: Influence of cyclosporine A-based immunosuppression on graft survival following kidney transplantation. (Courtesy of Prof Dr G. Opelz, Heidelberg.)
AZA = azathioprine; CYA = cyclosporine A; STE = steroids.

7.4.1 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 (CTS, 4).

7.4.2 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).

7.4.3 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 experience (5,9,11,15) with transplantations in urinary diversions than with transplantations in normal bladders.

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8. ABBREVIATIONS USED IN THE TEXT

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	anti-lymphocyte globulin
ATG	anti-thymocyte globulin
CAR	chronic allograft rejection
CCTT	Collaborative Clinical Trials in Transplantation (classification)
CDC	complement-dependent cytotoxicity test
CMV	cytomegalovirus
CT	computed tomography
CTS	Collaborative Transplant Study
CyA	cyclosporine A
DDT	dichlorodiphenyltrichlorethane
DRE	digital rectal examination
EBV	Epstein-Barr virus
EC	EuroCollins [solution]
EDTA	ethylenediaminetetra-acetic acid
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
HCV	hepatitis C
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
KTA	kidney transplant alone
LLDN	laparoscopic donor nephrectomy
LURD	living unrelated donor
MR	magnetic resonance
MRT	magnetic resonance tomography
NHBD	non-heart-beating donor
OKT3	anti-CD3 monoclonal antibody
PBS	phosphate-buffered sucrose
PRA	panel reactivity antibody
PSA	prostate-specific antigen
RCC	renal cell carcinoma
SPK	simultaneous pancreas and kidney transplantation
UW	University of Wisconsin [solution]
VATER	Vertebral/Vascular anomalies, Anal atresia, Tracheo-esophageal fistula, Esophageal atresia, Renal anomalies/Radical dysplasia